SPECIAL ISSUE: **HEREDITARY CANCERS** FEATURING CONFERENCE COVERAGE: **NCCN POLICY CONFERENCE**

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ALSO IN THIS ISSUE

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FREQUENT FIRST STOP. For women with breast or ovarian cancer considering their options, the first person consulted is often their obstetrician/gynecologist. Our conversation with Barbara S. Levy, MD, vice president for Health Policy, the American College of Obstetricians and Gynecologists, SP274.

FDA COLLABORATION. The chief medical officer of COTA Healthcare discusses upcoming work to explore the potential of real-world evidence and what it means for groups who are underrepresented in clinical trials, SP266.

HIGH-RISK POPULATIONS. The founder of a group that educates a population at high risk for *BRCA*-related cancers asks why more is not done to identify those most likely to develop the disease, SP270.

INSTITUTE FOR VALUE-BASED MEDICINE®. Regional Cancer Care Associates hosts the largest meeting yet to discuss how to deliver quality care under of the Oncology Care Model, SP272.

ALLISON

A NOBEL, AND NOW A MOVIE. The documentary, *Jim Allison: Breakthrough*, traces the unlikely story of the 2018 co-winner of the Nobel Prize in Physiology or Medicine, who defied skeptics in developing the first checkpoint inhibitor and launching the era of immuno-oncology, SP276.

REIMBURSEMENT

Forward-Thinking Insurers Adopt Genomics; Medicare Takes Perilous, Costly Leap Backward

Ellen Matloff, MS, CGC; Danielle Bonadies, MS, CGC; and Meagan Farmer, MBA, MS, CGC

THE FIELD OF GENETIC testing and genomics has exploded. Safe, high-quality prenatal tests that screen for chromosome abnormalities are now available through a simple blood draw via noninvasive prenatal screening. Ideally, prior to pregnancy, both men and women are candidates for carrier screening to determine if they carry mutations that would increase their risk of having a child with a recessive genetic condition. Germline genetic testing has expanded from rare diseases to high- and moderate-risk gene panels for more common conditions, including cancer and cardiac disease. Genetic testing on tumor tissue (somatic testing) is available for many cancers and can help guide treatment decisions based on which therapy will most likely lead to a response. Every day, more data are available to support the utility of genetic testing to offer smart, efficient, cost-effective patient care.

Several progressive insurance companies are recognizing the power of genetic testing to help their members achieve better health. One example can be seen in the arena of direct-to-consumer (DTC) genetic testing. More than 26 million consumers have chosen to undergo and pay for DTC testing via at-home spit kits from companies like 23andMe and Ancestry.[1] Some of these companies release genetic health information back to the consumer, and many can provide raw data files that the consumer can download and have interpreted by third-party literature retrieval services, like Promethease. None of these types of DTC tests are medical grade; therefore, they must be repeated on a new DNA sample in a clinical laboratory for verification before they can be used in medical care.[2,3]

CONTINUED ON SP282

ADVOCACY

The Impact of Germline Testing for Hereditary Cancer Postdiagnosis

Kelly Owens, PhD; Lisa Schlager; and Piri L. Welcsh, PhD

GERMLINE TESTING IS a key issue for the constituents of Facing Our Risk of Cancer Empowered (FORCE), a nonprofit organization focused on hereditary cancer. Its mission is to improve the lives of the millions of men, women, and families facing increased risk of breast, ovarian, pancreatic, prostate, colorectal, and endometrial cancers. Our community includes people with a *BRCA*, *ATM*, *PALB2*, *CHEK2*, *PTEN*, or other inherited gene mutation and those facing Lynch syndrome. We accomplish this mission through education, support, advocacy, and research.

Germline Mutations Can Raise Cancer Risk

Germline mutations are associated with an increased risk of a variety of cancers.

CONTINUED ON SP285

PROVIDER PERSPECTIVE

Genetic Oncology Testing Is Complex, but Coverage and Reimbursement Don't Have to Be

L. Patrick James, MD

LABORATORY SERVICES that identify genetic markers of cancer help predict future cancer, identify existing disease, and guide treatment decisions in oncology care. Despite this foundational role in cancer care, laboratory test services often face coverage and reimbursement pressures from health plans that struggle to evaluate the tests' clinical and economic value. Both oncologists and payers face an avalanche of information on diagnostic tests, which confuses treatment, coverage, and reimbursement decisions. Despite this, physicians and genetic counselors are willing to evaluate the data à la carte in the context of each patient. Genetic testing has quickly become an accepted aspect of mainstream medicine.[1]

Genetic testing holds clear value for oncology, but how do payers assess whether a test can provide enough value to warrant appropriate coverage and reimbursement for the right members?

CONTINUED ON SP288

AJMC® Managed Markets Network®
ACCC Association of Community Cancer Centers
AJMC® THE INSTITUTE FOR VALUE-BASED MEDICINE
COMMUNITY ONCOLOGY ALLIANCE COA

IBRANCE® (palbociclib) is the #1 PRESCRIBED FDA-approved oral combination treatment for HR+/HER2- MBC[1]

Indications

IBRANCE is indicated for the treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (MBC) in combination with:

- **an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in men, or**
- **fulvestrant in patients with disease progression following endocrine therapy**

Important Safety Information

Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis was observed in PALOMA-3. Inform patients to promptly report any fever.

Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Based on the mechanism of action, IBRANCE can cause **fetal harm**. Advise females of reproductive potential to use effective contraception during IBRANCE treatment and for at least 3 weeks after the last dose. IBRANCE may **impair fertility in males** and has the potential to cause genotoxicity. Advise male patients to consider sperm preservation before taking IBRANCE. Advise male patients with female partners of reproductive potential to use effective contraception during IBRANCE treatment and for 3 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise women **not to breastfeed** during IBRANCE treatment and for 3 weeks after the last dose because of the potential for serious adverse reactions in nursing infants.

The **most common adverse reactions (≥10%)** of any grade reported in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

The **most frequently reported Grade ≥3 adverse reactions (≥5%)** in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (66% vs 2%), leukopenia (25% vs 0%), infections (7% vs 3%), and anemia (5% vs 2%).

Lab abnormalities of any grade occurring in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were decreased WBC (97% vs 25%), decreased neutrophils (95% vs 20%), anemia (78% vs 42%), decreased platelets (63% vs 14%), increased aspartate aminotransferase (52% vs 34%), and increased alanine aminotransferase (43% vs 30%).

Unmatched experience in its class

4+ years
since initial FDA approval

13,000+ prescribers
have chosen IBRANCE[1]*

100,000+ patients
prescribed IBRANCE[1]*

*Estimated data, as of February 2019.[1]

Broad access for patients

IBRANCE is covered by[1]:

98%
of commercial plans†

100%
of Medicare Part D plans†

†Data current as of January 2019.[1]

See the latest information at **IBRANCEhcp.com**.

The **most common adverse reactions (≥10%)** of any grade reported in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (83% vs 4%), leukopenia (53% vs 5%), infections (47% vs 31%), fatigue (41% vs 29%), nausea (34% vs 28%), anemia (30% vs 13%), stomatitis (28% vs 13%), diarrhea (24% vs 19%), thrombocytopenia (23% vs 0%), vomiting (19% vs 15%), alopecia (18% vs 6%), rash (17% vs 6%), decreased appetite (16% vs 8%), and pyrexia (13% vs 5%).

The **most frequently reported Grade ≥3 adverse reactions (≥5%)** in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were neutropenia (66% vs 1%) and leukopenia (31% vs 2%).

Lab abnormalities of any grade occurring in **PALOMA-3** for IBRANCE plus fulvestrant vs placebo plus fulvestrant were decreased WBC (99% vs 26%), decreased neutrophils (96% vs 14%), anemia (78% vs 40%), decreased platelets (62% vs 10%), increased aspartate aminotransferase (43% vs 48%), and increased alanine aminotransferase (36% vs 34%).

Avoid concurrent use of **strong CYP3A inhibitors**. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of **strong CYP3A inducers**. The dose of **sensitive CYP3A substrates** with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

For patients with **severe hepatic impairment** (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg. The pharmacokinetics of IBRANCE **have not been studied** in patients **requiring hemodialysis**.

Please see Brief Summary on the following pages.

Reference: 1. Data on file. Pfizer Inc, New York, NY.

IBRANCE™
palbociclib | 125 mg capsules
FIRST IN CLASS

Brief Summary of Prescribing Information

IBRANCE® (palbociclib) capsules, for oral use
Initial U.S. Approval: 2015

INDICATIONS AND USAGE

IBRANCE is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine based therapy in postmenopausal women or in men; or
- fulvestrant in patients with disease progression following endocrine therapy.

DOSAGE AND ADMINISTRATION

Recommended Dose and Schedule. The recommended dose of IBRANCE is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. IBRANCE should be taken with food.

Administer the recommended dose of an aromatase inhibitor when given with IBRANCE. Please refer to the Full Prescribing Information for the aromatase inhibitor being used.

When given with IBRANCE, the recommended dose of fulvestrant is 500 mg administered on Days 1, 15, 29, and once monthly thereafter. Please refer to the Full Prescribing Information of fulvestrant.

Patients should be encouraged to take their dose of IBRANCE at approximately the same time each day.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). Capsules should not be ingested if they are broken, cracked, or otherwise not intact.

Pre/perimenopausal women treated with the combination IBRANCE plus fulvestrant therapy should also be treated with luteinizing hormone-releasing hormone (LHRH) agonists according to current clinical practice standards.

For men treated with combination IBRANCE plus aromatase inhibitor therapy, consider treatment with an LHRH agonist according to current clinical practice standards.

Dose Modification. If dose reduction is required, the first recommended dose reduction is to 100 mg/day and the second dose reduction is to 75 mg/day. If further dose reduction below 75 mg/day is required, discontinue the treatment.

Dose Modification and Management – Hematologic Toxicities[a]

Monitor complete blood counts prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated.

For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, monitor complete blood counts for subsequent cycles every 3 months, prior to the beginning of a cycle and as clinically indicated.

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of cycle: Withhold IBRANCE, repeat complete blood count monitoring within 1 week. When recovered to Grade ≤2, start the next cycle at the *same dose.* Day 15 of first 2 cycles: If Grade 3 on Day 15, continue IBRANCE at current dose to complete cycle and repeat complete blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. Consider dose reduction in cases of prolonged (>1 week) recovery from Grade 3 neutropenia or recurrent Grade 3 neutropenia on Day 1 of subsequent cycles.
Grade 3 neutropenia[b] with fever ≥38.5 ºC and/or infection	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose.*
Grade 4	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose.*

Grading according to CTCAE 4.0.
CTCAE=Common Terminology Criteria for Adverse Events; LLN=lower limit of normal.
[a] Table applies to all hematologic adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).
[b] Absolute neutrophil count (ANC): Grade 1: ANC < LLN - 1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3; Grade 3: ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3.

Dose Modification and Management – Non-Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-hematologic toxicity (if persisting despite optimal medical treatment)	Withhold until symptoms resolve to: • Grade ≤1; • Grade ≤2 (if not considered a safety risk for the patient) Resume at the *next lower dose*.

Grading according to CTCAE 4.0.

Refer to the Full Prescribing Information for coadministered endocrine therapy dose adjustment guidelines in the event of toxicity and other relevant safety information or contraindications.

Dose Modifications for Use With Strong CYP3A Inhibitors. Avoid concomitant use of strong CYP3A inhibitors and consider an alternative concomitant medication with no or minimal CYP3A inhibition. If patients must be coadministered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg once daily. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3 to 5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor.

Dose Modifications for Hepatic Impairment: No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

DOSING FORMS AND STRENGTHS

125 mg capsules: opaque hard gelatin capsules, size 0, with caramel cap and body, printed with white ink "Pfizer" on the cap, "PBC 125" on the body.

100 mg capsules: opaque hard gelatin capsules, size 1, with caramel cap and light orange body, printed with white ink "Pfizer" on the cap, "PBC 100" on the body.

75 mg capsules: opaque hard gelatin capsules, size 2, with light orange cap and body, printed with white ink "Pfizer" on the cap, "PBC 75" on the body.

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS

Neutropenia. Neutropenia was the most frequently reported adverse reaction in Study 1 (PALOMA-2) with an incidence of 80% and Study 2 (PALOMA-3) with an incidence of 83%. A Grade ≥3 decrease in neutrophil counts was reported in 66% of patients receiving IBRANCE plus letrozole in Study 1 and 66% of patients receiving IBRANCE plus fulvestrant in Study 2. In Study 1 and 2, the median time to first episode of any grade neutropenia was 15 days and the median duration of Grade ≥3 neutropenia was 7 days.

Monitor complete blood counts prior to starting IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across Studies 1 and 2. One death due to neutropenic sepsis was observed in Study 2. Physicians should inform patients to promptly report any episodes of fever.

Embryo-Fetal Toxicity. Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose.

ADVERSE REACTIONS

Clinical Studies Experience. Because clinical trials are conducted under varying conditions, the adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

Study 1: IBRANCE plus Letrozole. Patients with ER-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

The safety of IBRANCE (125 mg/day) plus letrozole (2.5 mg/day) versus placebo plus letrozole was evaluated in Study 1 (PALOMA-2). The data described below reflect exposure to IBRANCE in 444 out of 666 patients with ER-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in Study 1. The median duration of treatment for IBRANCE plus letrozole was 19.8 months while the median duration of treatment for placebo plus letrozole arm was 13.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus letrozole. No dose reduction was allowed for letrozole in Study 1.

Permanent discontinuation associated with an adverse reaction occurred in 43 of 444 (9.7%) patients receiving IBRANCE plus letrozole and in 13 of 222 (5.9%) patients receiving placebo plus letrozole. Adverse reactions leading to permanent discontinuation for patients receiving IBRANCE plus letrozole included neutropenia (1.1%) and alanine aminotransferase increase (0.7%).

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, infections, leukopenia, fatigue, nausea, alopecia, stomatitis, diarrhea, anemia, rash, asthenia, thrombocytopenia, vomiting, decreased appetite, dry skin, pyrexia, and dysgeusia.

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leukopenia, infections, and anemia.

Adverse Reactions (≥10%) in Study 1

Adverse Reaction	IBRANCE + Letrozole (N=444)			Placebo + Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[a]	60[b]	6	1	42	3	0
Blood and lymphatic system disorders						
Neutropenia	80	56	10	6	1	1
Leukopenia	39	24	1	2	0	0
Anemia	24	5	<1	9	2	0
Thrombocytopenia	16	1	<1	1	0	0
Metabolism and nutrition disorders						
Decreased appetite	15	1	0	9	0	0
Nervous system disorders						
Dysgeusia	10	0	0	5	0	0
Gastrointestinal disorders						
Stomatitis[c]	30	1	0	14	0	0
Nausea	35	<1	0	26	2	0
Diarrhea	26	1	0	19	1	0
Vomiting	16	1	0	17	1	0
Skin and subcutaneous tissue disorders						
Alopecia	33[d]	N/A	N/A	16[e]	N/A	N/A
Rash[f]	18	1	0	12	1	0
Dry skin	12	0	0	6	0	0
General disorders and administration site conditions						
Fatigue	37	2	0	28	1	0
Asthenia	17	2	0	12	0	0
Pyrexia	12	0	0	9	0	0

Grading according to CTCAE 3.0.
N=number of patients; N/A=not applicable
[a] Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.
[b] Most common infections (>1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, oral herpes, sinusitis, rhinitis, bronchitis, influenza, pneumonia, gastroenteritis, conjunctivitis, herpes zoster, pharyngitis, cellulitis, cystitis, lower respiratory tract infection, tooth infection, gingivitis, skin infection, gastroenteritis viral, respiratory tract infection, respiratory tract infection viral, and folliculitis.
[c] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oral discomfort, oropharyngeal pain, and stomatitis.
[d] Grade 1 events – 30%; Grade 2 events – 3%.
[e] Grade 1 events – 15%; Grade 2 events – 1%.
[f] Rash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, and toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving Ibrance plus letrozole in Study 1 included alanine aminotransferase increased (9.9%), aspartate aminotransferase increased (9.7%), epistaxis (9.2%), lacrimation increased (5.6%), dry eye (4.1%), vision blurred (3.6%), and febrile neutropenia (2.5%).

Laboratory Abnormalities in Study 1

Laboratory Abnormality	IBRANCE + Letrozole (N=444)			Placebo plus Letrozole (N=222)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	97	35	1	25	1	0
Neutrophils decreased	95	56	12	20	1	1
Anemia	78	6	0	42	2	0
Platelets decreased	63	1	1	14	0	0
Aspartate aminotransferase increased	52	3	0	34	1	0
Alanine aminotransferase increased	43	2	<1	30	0	0

N=number of patients; WBC=white blood cells.

Study 2: IBRANCE plus Fulvestrant. Patients with HR-positive, HER2-negative advanced or metastatic breast cancer who have had disease progression on or after prior adjuvant or metastatic endocrine therapy

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in Study 2 (PALOMA-3). The data described below reflect exposure to IBRANCE in 345 out of 517 patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at

least 1 dose of IBRANCE plus fulvestrant in Study 2. The median duration of treatment for IBRANCE plus fulvestrant was 10.8 months while the median duration of treatment for placebo plus fulvestrant arm was 4.8 months.

Dose reductions due to an adverse reaction of any grade occurred in 36% of patients receiving IBRANCE plus fulvestrant. No dose reduction was allowed for fulvestrant in Study 2.

Permanent discontinuation associated with an adverse reaction occurred in 19 of 345 (6%) patients receiving IBRANCE plus fulvestrant, and in 6 of 172 (3%) patients receiving placebo plus fulvestrant. Adverse reactions leading to discontinuation for those patients receiving IBRANCE plus fulvestrant included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

The most common adverse reactions (≥10%) of any grade reported in patients in the IBRANCE plus fulvestrant arm by descending frequency were neutropenia, leukopenia, infections, fatigue, nausea, anemia, stomatitis, diarrhea, thrombocytopenia, vomiting, alopecia, rash, decreased appetite, and pyrexia.

The most frequently reported Grade ≥3 adverse reactions (≥5%) in patients receiving IBRANCE plus fulvestrant in descending frequency were neutropenia and leukopenia.

Adverse Reactions (≥10%) in Study 2

Adverse Reaction	IBRANCE + Fulvestrant (N=345)			Placebo + Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[a]	47[b]	3	1	31	3	0
Blood and lymphatic system disorders						
Neutropenia	83	55	11	4	1	0
Leukopenia	53	30	1	5	1	1
Anemia	30	3	0	13	2	0
Thrombocytopenia	23	2	1	0	0	0
Metabolism and nutrition disorders						
Decreased appetite	16	1	0	8	1	0
Gastrointestinal disorders						
Nausea	34	0	0	28	1	0
Stomatitis[c]	28	1	0	13	0	0
Diarrhea	24	0	0	19	1	0
Vomiting	19	1	0	15	1	0
Skin and subcutaneous tissue disorders						
Alopecia	18[d]	N/A	N/A	6[e]	N/A	N/A
Rash[f]	17	1	0	6	0	0
General disorders and administration site conditions						
Fatigue	41	2	0	29	1	0
Pyrexia	13	<1	0	5	0	0

Grading according to CTCAE 4.0.

[a] Infections includes all reported preferred terms (PTs) that are part of the System Organ Class Infections and infestations.

[b] Most common infections (>1%) include: nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, rhinitis, influenza, conjunctivitis, sinusitis, pneumonia, cystitis, oral herpes, respiratory tract infection, gastroenteritis, tooth infection, pharyngitis, eye infection, herpes simplex, and paronychia.

[c] Stomatitis includes: aphthous stomatitis, cheilitis, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal discomfort, oropharyngeal pain, stomatitis.

[d] Grade 1 events – 17%; Grade 2 events – 1%.

[e] Grade 1 events – 6%.

[f] Rash includes: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform, toxic skin eruption.

Additional adverse reactions occurring at an overall incidence of <10.0% of patients receiving IBRANCE plus fulvestrant in Study 2 included asthenia (7.5%), aspartate aminotransferase increased (7.5%), dysgeusia (6.7%), epistaxis (6.7%), lacrimation increased (6.4%), dry skin (6.1%), alanine aminotransferase increased (5.8%), vision blurred (5.8%), dry eye (3.8%), and febrile neutropenia (0.9%).

Laboratory Abnormalities in Study 2

Laboratory Abnormality	IBRANCE + Fulvestrant (N=345)			Placebo + Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
Aspartate aminotransferase increased	43	4	0	48	4	0
Alanine aminotransferase increased	36	2	0	34	0	0

Postmarketing Experience. The following adverse reactions have been identified during post-approval use of IBRANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Respiratory disorders*: Interstitial lung disease (ILD)/non-infectious pneumonitis.

Male patients with HR-positive, HER2-negative advanced or metastatic breast cancer

Based on limited data from postmarketing reports and electronic health records, the safety profile for men treated with IBRANCE is consistent with the safety profile in women treated with IBRANCE.

DRUG INTERACTIONS

Palbociclib is primarily metabolized by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. In vivo, palbociclib is a time-dependent inhibitor of CYP3A.

Effect of CYP3A Inhibitors. Coadministration of a strong CYP3A inhibitor (itraconazole) increased the plasma exposure of palbociclib in healthy subjects by 87%. Avoid concomitant use of strong CYP3A inhibitors (e.g., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole). Avoid grapefruit or grapefruit juice during IBRANCE treatment. If coadministration of IBRANCE with a strong CYP3A inhibitor cannot be avoided, reduce the dose of IBRANCE.

Effect of CYP3A Inducers. Coadministration of a strong CYP3A inducer (rifampin) decreased the plasma exposure of palbociclib in healthy subjects by 85%. Avoid concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampin, carbamazepine, enzalutamide, and St John's Wort).

Drugs That May Have Their Plasma Concentrations Altered by Palbociclib. Coadministration of midazolam with multiple doses of IBRANCE increased the midazolam plasma exposure by 61%, in healthy subjects, compared with administration of midazolam alone. The dose of the sensitive CYP3A substrate with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus) may need to be reduced as IBRANCE may increase their exposure.

USE IN SPECIFIC POPULATIONS

Pregnancy. Based on findings from animal studies and its mechanism of action, IBRANCE can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of palbociclib to pregnant rats and rabbits during organogenesis resulted in embryo-fetal toxicity at maternal exposures that were ≥4 times the human clinical exposure based on AUC. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

In a fertility and early embryonic development study in female rats, palbociclib was administered orally for 15 days before mating through to Day 7 of pregnancy, which did not cause embryo toxicity at doses up to 300 mg/kg/day with maternal systemic exposures approximately 4 times the human exposure (AUC) at the recommended dose.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses up to 300 mg/kg/day and 20 mg/kg/day palbociclib, respectively, during the period of organogenesis. The maternally toxic dose of 300 mg/kg/day was fetotoxic in rats, resulting in reduced fetal body weights. At doses ≥100 mg/kg/day in rats, there was an increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra). At the maternally toxic dose of 20 mg/kg/day in rabbits, there was an increased incidence of skeletal variations, including small phalanges in the forelimb. At 300 mg/kg/day in rats and 20 mg/kg/day in rabbits, the maternal systemic exposures were approximately 4 and 9 times the human exposure (AUC) at the recommended dose, respectively.

CDK4/6 double knockout mice have been reported to die in late stages of fetal development (gestation Day 14.5 until birth) due to severe anemia. However, knockout mouse data may not be predictive of effects in humans due to differences in degree of target inhibition.

Lactation. There is no information regarding the presence of palbociclib in human milk, nor its effects on milk production or the breastfed infant. Because of the potential for serious adverse reactions in breastfed infants from IBRANCE, advise a lactating woman not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

Females and Males of Reproductive Potential. Based on animal studies, IBRANCE can cause fetal harm when administered to a pregnant woman. Females of reproductive potential should have a pregnancy test prior to starting treatment with IBRANCE. IBRANCE can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 weeks after the last dose. Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for 3 months after the last dose. Based on animal studies, IBRANCE may impair fertility in males of reproductive potential.

Pediatric Use. The safety and efficacy of IBRANCE in pediatric patients have not been studied.

Altered glucose metabolism (glycosuria, hyperglycemia, decreased insulin) associated with changes in the pancreas (islet cell vacuolation), eye (cataracts, lens degeneration), kidney (tubule vacuolation, chronic progressive nephropathy) and adipose tissue (atrophy) were identified in a 27 week repeat-dose toxicology study in rats that were immature at the beginning of the studies and were most prevalent in males at oral palbociclib doses ≥30 mg/kg/day (approximately 11 times the adult human exposure [AUC] at the recommended dose). Some of these findings (glycosuria/hyperglycemia, pancreatic islet cell vacuolation, and kidney tubule vacuolation) were present with lower incidence and severity in a 15 week repeat-dose toxicology study in immature rats. Altered glucose metabolism or associated changes in the pancreas, eye, kidney and adipose tissue were not identified in a 27-week repeat-dose toxicology study in rats that were mature at the beginning of the study and in dogs in repeat-dose toxicology studies up to 39 weeks duration.

Toxicities in teeth independent of altered glucose metabolism were observed in rats. Administration of 100 mg/kg palbociclib for 27 weeks (approximately 15 times the adult human exposure [AUC] at the recommended dose) resulted in abnormalities in growing incisor teeth (discolored, ameloblast degeneration/necrosis, mononuclear cell infiltrate). Other toxicities of potential concern to pediatric patients have not been evaluated in juvenile animals.

Geriatric Use. Of 444 patients who received IBRANCE in Study 1, 181 patients (41%) were ≥65 years of age and 48 patients (11%) were ≥75 years of age. Of 347 patients who received IBRANCE in Study 2, 86 patients (25%) were ≥65 years of age and 27 patients (8%) were ≥75 years of age. No overall differences in safety or effectiveness of IBRANCE were observed between these patients and younger patients.

Hepatic Impairment. No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Based on a pharmacokinetic trial in subjects with varying degrees of hepatic function, the palbociclib unbound exposure (unbound AUC_{INF}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment, respectively, relative to subjects with normal hepatic function. Peak palbociclib unbound exposure (unbound C_{max}) increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function.

Review the Full Prescribing Information for the aromatase inhibitor or fulvestrant for dose modifications related to hepatic impairment.

Renal Impairment. No dose adjustment is required in patients with mild, moderate, or severe renal impairment (CrCl >15 mL/min). Based on a pharmacokinetic trial in subjects with varying degrees of renal function, the total palbociclib exposure (AUC_{INF}) increased by 39%, 42%, and 31% with mild (60 mL/min ≤ CrCl <90 mL/min), moderate (30 mL/min ≤ CrCl <60 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, relative to subjects with normal renal function. Peak palbociclib exposure (C_{max}) increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. The pharmacokinetics of palbociclib have not been studied in patients requiring hemodialysis.

OVERDOSAGE

There is no known antidote for IBRANCE. The treatment of overdose of IBRANCE should consist of general supportive measures.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression/Infection

- Advise patients to immediately report any signs or symptoms of myelosuppression or infection, such as fever, chills, dizziness, shortness of breath, weakness or any increased tendency to bleed and/or to bruise.

Drug Interactions

- Grapefruit may interact with IBRANCE. Patients should not consume grapefruit products while on treatment with IBRANCE.
- Inform patients to avoid strong CYP3A inhibitors and strong CYP3A inducers.
- Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products.

Dosing and Administration

- Advise patients to take IBRANCE with food.
- If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE capsules should be swallowed whole (do not chew, crush or open them prior to swallowing). No capsule should be ingested if it is broken, cracked, or otherwise not intact.
- Pre/perimenopausal women treated with IBRANCE should also be treated with LHRH agonists.

Pregnancy, Lactation, and Infertility

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment with IBRANCE therapy and for at least 3 weeks after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment with IBRANCE and for at least 3 months after the last dose.

Lactation

- Advise women not to breastfeed during treatment with IBRANCE and for 3 weeks after the last dose.

Infertility

- Inform males of reproductive potential that IBRANCE may cause infertility and to consider sperm preservation before taking IBRANCE.

Rx only

This brief summary is based on IBRANCE® (palbociclib) Prescribing Information LAB-0723-7.0, Rev. 04/2019.

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EBOncology

SPECIAL ISSUE /Hereditary Cancers

AUGUST 2019

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EBOncology

FROM THE EDITOR-IN-CHIEF

Within Ourselves

The fault, dear Brutus, is not in our stars, but in ourselves...
Julius Caesar (I, ii, 140-141)


ALVARNAS

SINCE THE INITIAL COMPLETION of the human genomic project in April 2003, our knowledge of the genetic underpinnings of cancer has expanded at a rate that is unprecedented in the history of medicine. We now have a much deeper appreciation that the genesis, development, growth, and spread of a number of cancers is not governed by happenstance, bad luck, or random biology. Cancer, instead, has a deep set of genetic underpinnings that are inherited or acquired due to environmental exposure, aging, viral infection, or the acquisition of a specific set of genetic mutations. *Somatic mutations* are those that exist specifically within the patient's cancer cells, whereas *germline mutations* are those that are inherited and found within both cancer cells and healthy cells within the patient. The Cancer Gene Census publishes a catalogue of those genes that are known to play a potential role in cancer. The authors note:

Currently, more than 1% of all human genes are implicated via mutation in cancer. Of these, approximately 90% contain somatic mutations in cancer, 20% bear germline mutations that predispose an individual to cancer, and 10% show both.

The National Cancer Institute notes that up to 10% of all cancers result from inherited genetic mutations. In a 2018 study, researchers using a high-throughput method of gene identification called Capture Hi-C described more than 110 gene mutations that are associated with the development of breast cancer. A genetic basis for cancer has now been described for an enormous number of tumor types. This number, and the continued identification of implicated genes is growing at an enormous pace.

This knowledge should lead us to 3 conclusions:

1. Cancer is knowable at a level that was unimaginable prior to the availability of genetic/genomic testing.
2. This knowledge may serve as the basis for better care that is targeted upon the individual patient, rather than a generic patient with that tumor type. Genetic data for an individual may play a profoundly important role in risk determination, development of therapeutic strategy, and the selection of available targeted anticancer agents.
3. This knowledge will play a central role in the development of new targeted therapeutics for patients with similar genetic mutations.

These conclusions form the basis for the paradigm of *precision medicine*. Moving from a conceptual paradigm toward one that helps patients and families find better answers for their cancer journey involves creating better systems for testing and processing genetic data from a patient and translating it into practical decision-making and care support. Delivering this sustainably and equitably will require a scalable system linked to a financial model that aligns reimbursement with more effective decision support and care delivery.

In this month's issue of *Evidence-Based Oncology*™, we look at the importance of cancer genetic testing and examine how precision medicine can be delivered more effectively and sustainably to patients affected by cancer. Of note, authors from FORCE explore the impact of germline testing for hereditary cancer after diagnosis. Loren Corduck of Oneinforty describes how genetic testing may spare patients unnecessary suffering while improving survival.

The ability to know, understand, and defeat cancer lies within ourselves. It is not a matter of luck or fate that determines the best path toward a cure. As advances in genetic testing, high-throughput computing (which allows us to identify relevant gene mutations from those that are irrelevant), and anticancer therapeutic research lead to more solutions for patients, the next step in this extraordinary evolution in cancer care is for us to create better systems to ensure that we can deliver these cures equitably and effectively to all of those in need. The bones of this system are here, for us to behold. ◆

Joseph Alvarnas, MD
Editor-in-Chief

EDITORIAL MISSION

To present policy makers, payers, and providers with the clinical, pharmacoeconomic, and regulatory information they need to improve efficiency and outcomes in cancer care.

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PHOTO CREDIT: UNCOMMON PRODUCTIONS

FROM THE CHAIRMAN

We Have the Tools to Prevent Hereditary Cancers. Now We Need Coverage.

THE NEWS "YOU HAVE CANCER" is life changing for any individual, but sometimes it changes life for an entire family. We have known for some time that breast or ovarian cancer can result from a *BRCA* gene mutation; when one of these cancers happens to a mother or sister or daughter, the rest of the family must receive genetic testing so that each person can make decisions based on the likelihood of cancer affecting their life, too. These decisions are not easy, but we are fortunate to live in a time when we have the technology and the expertise of genetic counselors, who can assist families in shared decision making.

Family decisions become fraught when an insurer determines that a person at risk of hereditary cancer must wait for the disease to develop instead of being tested, which would open the door to prophylactic surgery if mutations are found. Yet, as we learn in this issue from genetic counselor Ellen Matloff, MS, CGC, and her colleagues, this is what Medicare does. Matloff has spent years on the frontiers of this field, advocating for patients to have a variety of testing options. Today she has a new cause—CMS must recognize genetic counselors as providers, and tests must be covered when they can *prevent* cancer. We are learning more and more about the value of testing in cancer care—this past spring, the National Comprehensive Cancer Network conference featured updates to testing guidelines across multiple cancers. We are learning about the importance of testing men for *BRCA* mutations and the role of these mutations in prostate and pancreatic cancer.[1,2]

Matloff et al report that many commercial insurers see the value of preventing cancer through genetic testing and counseling. Medicare's outdated policy and its initial bungling of the national coverage determination on next-generation sequencing (NGS) could cost taxpayers plenty if there are missed opportunities to prevent or properly treat cancers as the population ages. Commentators have noted that not all NGS technologies are the same, and CMS could significantly harm precision medicine with poor reimbursement policy.[3]

CMS has the chance to get it right before its policy becomes final. Testing protocols that miss preventable cancers come at a price no one should pay. ◆

Sincerely,

Mike Hennessy, Sr
CHAIRMAN AND CEO

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XPOVIO™

(selinexor) 20 mg tablet

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INDICATION

XPOVIO is indicated in combination with dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Please see additional Important Safety Information continued on the following page and XPOVIO Full Prescribing Information on XPOVIO.com.

IMPORTANT SAFETY INFORMATION

XPOVIO™ (selinexor) 20 mg tablet

Thrombocytopenia
XPOVIO can cause thrombocytopenia, leading to potentially fatal hemorrhage. Thrombocytopenia was reported as an adverse reaction in 74% of patients, and severe (Grade 3-4) thrombocytopenia occurred in 61% of patients treated with XPOVIO. The median time to onset of the first event was 22 days. Bleeding occurred in 23% of patients with thrombocytopenia, clinically significant bleeding occurred in 5% of patients with thrombocytopenia and fatal hemorrhage occurred in <1% of patients.

Monitor platelet counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Institute platelet transfusion and/or other treatments as clinically indicated. Monitor patients for signs and symptoms of bleeding and evaluate promptly. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Neutropenia
XPOVIO can cause neutropenia, potentially increasing the risk of infection. Neutropenia was reported as an adverse reaction in 34% of patients, and severe (Grade 3-4) neutropenia occurred in 21% of patients treated with XPOVIO. The median time to onset of the first event was 25 days. Febrile neutropenia was reported in 3% of patients.

Obtain neutrophil counts at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Monitor patients for signs and symptoms of concomitant infection and evaluate promptly. Consider supportive measures including antimicrobials for signs of infection and use of growth factors (e.g., G-CSF). Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Gastrointestinal Toxicity
Gastrointestinal toxicities occurred in patients treated with XPOVIO.

Nausea/Vomiting
Nausea was reported as an adverse reaction in 72% of patients, and Grade 3 nausea occurred in 9% of patients treated with XPOVIO. The median time to onset of the first nausea event was 3 days.

Vomiting was reported in 41% of patients, and Grade 3 vomiting occurred in 4% of patients treated with XPOVIO. The median time to onset of the first vomiting event was 5 days.

Provide prophylactic 5-HT3 antagonists and/or other anti-nausea agents, prior to and during treatment with XPOVIO. Manage nausea/vomiting by dose interruption, reduction, and/or discontinuation. Administer intravenous fluids and replace electrolytes to prevent dehydration in patients at risk. Use additional anti-nausea medications as clinically indicated.

Diarrhea
Diarrhea was reported as an adverse reaction in 44% of patients, and Grade 3 diarrhea occurred in 6% of patients treated with XPOVIO. The median time to onset of diarrhea was 15 days.

Manage diarrhea by dose modifications and/or standard anti-diarrheal agents; administer intravenous fluids to prevent dehydration in patients at risk.

Anorexia/Weight Loss
Anorexia was reported as an adverse reaction in 53% of patients, and Grade 3 anorexia occurred in 5% of patients treated with XPOVIO. The median time to onset of anorexia was 8 days.

Weight loss was reported as an adverse reaction in 47% of patients, and Grade 3 weight loss occurred in 1% of patients treated with XPOVIO. The median time to onset of weight loss was 15 days.

Monitor patient weight at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Manage anorexia and weight loss with dose modifications, appetite stimulants, and nutritional support.

Please see additional Important Safety Information continued on the following page and XPOVIO Full Prescribing Information on XPOVIO.com.

IMPORTANT SAFETY INFORMATION (cont'd)

XPOVIO™ (selinexor) 20 mg tablet

Hyponatremia

XPOVIO can cause hyponatremia; 39% of patients treated with XPOVIO experienced hyponatremia, 22% of patients experienced Grade 3 or 4 hyponatremia. The median time to onset of the first event was 8 days.

Monitor sodium level at baseline, during treatment, and as clinically indicated. Monitor more frequently during the first two months of treatment. Correct sodium levels for concurrent hyperglycemia (serum glucose >150 mg/dL) and high serum paraprotein levels. Treat hyponatremia per clinical guidelines (intravenous saline and/or salt tablets), including dietary review. Interrupt and/or reduce dose, or permanently discontinue based on severity of adverse reaction.

Infections

In patients receiving XPOVIO, 52% of patients experienced any grade of infection. Upper respiratory tract infection of any grade occurred in 21%, pneumonia in 13%, and sepsis in 6% of patients. Grade ≥3 infections were reported in 25% of patients, and deaths resulting from an infection occurred in 4% of patients. The most commonly reported Grade ≥3 infections were pneumonia in 9% of patients, followed by sepsis in 6%. The median time to onset was 54 days for pneumonia and 42 days for sepsis. Most infections were not associated with neutropenia and were caused by non-opportunistic organisms.

Neurological Toxicity

Neurological toxicities occurred in patients treated with XPOVIO.

Neurological adverse reactions including dizziness, syncope, depressed level of consciousness, and mental status changes (including delirium and confusional state) occurred in 30% of patients, and severe events (Grade 3-4) occurred in 9% of patients treated with XPOVIO. Median time to the first event was 15 days.

Optimize hydration status, hemoglobin level, and concomitant medications to avoid exacerbating dizziness or mental status changes.

Embryo-Fetal Toxicity

Based on data from animal studies and its mechanism of action, XPOVIO can cause fetal harm when administered to a pregnant woman. Selinexor administration to pregnant animals during organogenesis resulted in structural abnormalities and alterations to growth at exposures below those occurring clinically at the recommended dose.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with a female partner of reproductive potential to use effective contraception during treatment with XPOVIO and for 1 week after the last dose.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥20%) are thrombocytopenia, fatigue, nausea, anemia, decreased appetite, decreased weight, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dyspnea, and upper respiratory tract infection.

The treatment discontinuation rate due to adverse reactions was 27%; 53% of patients had a reduction in the XPOVIO dose, and 65.3% had the dose of XPOVIO interrupted. The most frequent adverse reactions requiring permanent discontinuation in 4% or greater of patients who received XPOVIO included fatigue, nausea, and thrombocytopenia. The rate of fatal adverse reactions was 8.9%.

Of the 202 patients with RRMM who received XPOVIO, 49% were 65 years of age and over, while 11% were 75 years of age and over. No overall difference in effectiveness was observed in patients over 65 years of age, including patients over 75 years of age, when compared with younger patients. When comparing patients 75 years of age and older to younger patients, older patients had a higher incidence of discontinuation due to an adverse reaction (44% vs 27%), higher incidence of serious adverse reactions (70% vs 58%), and higher incidence of fatal adverse reactions (17% vs 9%).

Please see XPOVIO Full Prescribing Information.

Reference: XPOVIO (selinexor) [package insert]. Newton, MA: Karyopharm Therapeutics; July 2019.

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COTA Collaboration: Helping FDA Figure Out What's Possible, What's Not in Embrace of Real-World Evidence

A Conversation With Chief Medical Officer Andrew Norden, MD, MPH, MBA

Mary Caffrey

WHEN IT COMES TO generating evidence that leads to a drug approval, the randomized controlled trial (RCT) is the gold standard. The first published trial appeared in the literature more than 70 years ago,[1] and over the past 30 years, the scientific community has developed the principles of evidence-based medicine,[2] in which RCT results inform clinical practice guidelines.

ANDREW NORDEN, MD, MPH, MBA

But the problem with the gold standard, as Andrew Norden, MD, MPH, MBA, sees it, is that too many people get left out. Norden, a neurologist and neuro-oncologist who is the chief medical officer at COTA Healthcare, described a well-documented problem with current RCTs: The typical participant in a clinical trial for a cancer drug "is more often white, more often male, more often wealthy, and certainly more often healthy" than the average person with cancer.[3] That means physicians need some other way to gauge how new drugs might work on the other people who come to their clinics.

Enter real-world evidence (RWE), which is the domain of COTA, a company founded 8 years ago by cancer doctors and data scientists with the idea of harnessing the vast amounts of electronic health records (EHRs) that were accumulating, albeit in a disorganized way. COTA's mission is to make sense of the noise so that cancer doctors can use what the data tell them about other cancer patients just like the one in front of them. The company is known for the development of the COTA Nodal Address (CNA), which condenses patient attributes into a digital code that allows providers or payers to evaluate cancer patients with similar characteristics in patient groupings.[3]

In an interview with *Evidence-Based Oncology*™ (*EBO*), Norden emphasized that COTA is not looking to eliminate RCTs. But by unlocking the secrets of the data sets in EHRs, real-world data can "extend" the findings of the RCT, as Norden puts it, and offer researchers, clinicians, and the FDA insight into how drugs work in populations that don't find their way into clinical trials.

This could mean insight about patients who are poor, are racial minorities, or have chronic conditions. "As a physician, I strongly advocate for the inclusion of patients from all those groups," Norden said. "I think it's a real disservice that they tend not to be [included]. Thankfully, a lot of folks are working on that problem—I want them to continue that work. But in the meantime, there are lessons we can learn about the applicability of clinical trial findings to patients who may fall into underrepresented groups in the clinical trial world."

Congress recognized this problem in 2016 when it passed the 21st Century Cures Act, which directed the FDA to develop a framework for using RWE in the course of drug regulation.[4] The agency has responded: It published a framework in December 2018[5] and in May 2019 published guidance documents on EHR data in clinical investigations and use of RWE in decision making for medical devices, as well as a draft document on submitting RWE for drugs and biologics.[6]

At that time, the FDA also announced it would join with COTA in a 2-year research and collaboration agreement: Starting with breast cancer, the federal regulator and the healthcare data and analytics company would create a study protocol to guide approaches to handling treatment variation within subpopulations and how RWE might be used to guide regulators.[7]

COTA comes to the partnership with several collaborations in hand. It has a pilot project with New Jersey's largest insurer, Horizon Blue Cross Blue Shield,[8] and joined several other technology and data sources in a project with Friends of Cancer Research.[9] In July 2018, the Friends project published a white paper demonstrating several approaches to evaluating real-world end points using a scenario that evaluated patients with advanced non–small cell lung cancer treated with immune checkpoint inhibitors. The paper explored several end points—real-world progression-free survival, real-world time to progression, time to next treatment, time to treatment discontinuation, and overall survival (OS).

In the interview, Norden said that the project's participants took different approaches, but the good news for RWE is: "We actually came to the same answers."

According to the white paper, "The pilot project demonstrated that several extractable end points from EHR and claims data correlate with OS. Further validation is required to determine whether these end points are reliable surrogates for OS outside of a traditional clinical trial and whether they can support regulatory and payer decision making."[9]

What follows is *EBO*'s discussion with Norden on the advancement of the CNA, plans for the FDA collaboration, and the potential for RWE (edited for clarity).

EBO: How has the CNA used data from EHRs to advance patient care to date, and how have clinicians responded to CNA?

Norden: The COTA Nodal Address is a unique way of grouping patients; in fact, we believe there isn't another cohorting mechanism that takes into account cancer-specific information the way the CNA does. We think about it like a turbocharged *ICD-10* [*International Classification of Diseases, 10th Revision*] code. It's based on today's conception of precision medicine, which says that you need to know a fair amount of clinical detail about any individual cancer patient to know what the right treatment is, estimate that patient's prognosis, and predict cost of care. The CNA brings together all the attributes that influence outcomes, treatment decisions, and costs into a single digital code.

Ultimately, when the CNAs are assigned and you have 2 patients—perhaps in different geographies or with different physicians—if they have the [same] CNA, there's no clinically proven reason those patients should be treated differently. You can use the CNA to identify unwarranted variation in treatment decisions or in costs. The information you glean from doing this analysis lets you develop an improvement plan around those things—it lets you target unwarranted variation based on specific, clinically defined cohorts that physicians understand.

EBO: How large is COTA's network currently, and how does COTA intend to expand its network between now and 2020?

Norden: The COTA network is growing quickly. Patients represented are primarily from the East Coast, with a particular concentration from the Mid-Atlantic [region] and Florida. We are looking to expand on to the West Coast in 2019. One of the valuable aspects of COTA's data set is that we have significant representation of patients who are treated in academic centers and community centers. We think that makes our data set more representative of the population at large. We know that in the United States, a lot of patients—maybe 80% or more—are treated in community centers. We think it's really important that a real-world data set represent the patients regardless of the site of service. Often, we find interesting trends that relate to the way patients are cared for in one setting or the other.

***EBO:* Can you describe the broad outlines of COTA's collaboration with FDA and how it fits into the agency's commitment to incorporate RWE into decision making?**

Norden: The FDA has clearly signaled in the last year or more that [the agency is] interested in the potential to use real-world data—and the evidence generated from that data—for regulatory decision making. The way I view this personally is that we have an enormous amount of information being entered into electronic medical records [EMRs].

Now, it's a fact that EMRs were not designed from the get-go to efficiently enable analysis of data across a population of patients. That's true, but we're developing techniques—we at COTA and others in industry and academia—that allow one to efficiently extract and analyze it. In my view, it would be foolish not to take advantage of that data when we want to understand how cancer care is delivered in the United States. The FDA seems to be very much on board with that line of thinking.

That's not to say that the FDA or COTA is advocating for the end of clinical trials.… That is not at all the viewpoint that COTA espouses. In fact, we think that real-world evidence, derived from the EMR and other sources, is a great complement to clinical trial data.

There's no argument about the reality that clinical trial patients are highly selected, they are wealthier, they tend to be healthier, and they tend to be more often white and more often male in many cases than in the community of cancer patients at large. So, the value of real-world evidence is that you can look to extend the findings of clinical trials to a more broadly representative patient group. It's also the case that there may be a small set of scenarios where real-world evidence could take the place of a clinical trial. I don't think that's true broadly, but I think there are some scenarios where it's true.

It may be true in rare diseases in which a clinical trial is unlikely to happen anyway because there just aren't enough patients. It may be true in a setting where multiple drugs have already been approved and there's no partner interested in funding a head-to-head comparison study. It may be true in a scenario where a drug has entered usage and has a very large effect size, and we can see clearly in real-world data that it's superior to an existing agent.

There are these scenarios, but for the most part, the value in my mind of real-world evidence is that it can extend the findings of clinical trials; [it can] help us confirm that what we learned in a clinical trial is, in fact, true in patients who are somewhat different from the population represented in the clinical trial.

I think that's what the FDA is looking to do in the collaboration with us. The truth is that today, the methods and the capacity of real-world evidence to answer important questions are somewhat immature. We haven't proved this yet. So, the FDA, like all of us in this industry, is looking to learn how this might work, and COTA is an important part of driving that forward.

[The FDA is] looking to learn what kinds of elements our data can capture, how we capture those data elements, how confident we can be that they are accurate, and then look to see what's possible—what clinical trial findings can we extend, in what scenarios might we be able to replace clinical trials, because I do think there are selected circumstances where that's possible—and then let the science take us where it will.

This is a scientific relationship between COTA and the FDA. It's not a commercial relationship—we're not looking to approve a new drug. We're looking to show what is possible and what is not possible. It's in the interest of all the healthcare stakeholders to do this work, because there's great potential for real-world data to accelerate the findings of clinical trials and to get drugs to market faster when there are strong data in favor of their use.

***EBO:* What specific milestones and deliverables should we look for as the collaboration proceeds?**

Norden: At the moment, COTA and the FDA are busy talking about precisely what our work together will entail. We have agreed to start with breast cancer, because it's a common disease with substantial areas of controversy and some areas of important unmet need—and a lot of active drugs in development. But we have not yet settled on the specifics of what we will provide.

I think what you can expect is that as this work ramps up, we will submit abstracts to meetings and present posters and oral presentations. We anticipate presenting manuscripts so that the scientific community at large can learn about our work. The specific scientific deliverables and timelines are still under discussion.

***EBO:* During this year's annual meeting of the American Society of Clinical Oncology, there was a presentation on the closure of the treatment gap in cancer care that was attributed to improved access under the Affordable Care Act.[10] What kind of treatment improvements do you foresee by closing the information gaps for groups that are not represented in clinical trials?**

Norden: I do think the work that COTA and others involved in aggregating and curating real-world data and generating evidence from that data can be valuable from the standpoint of reducing disparities in cancer care. We know that for a long time, clinical trial populations have been dominated by patients who tend to be more often white, more often male, more often wealthy, and certainly more often healthy than the average patient with cancer. And yet, a lot of information about patients who are perhaps more representative of the population at large is captured in EMRs today.

So, in COTA's view, one of the key advantages to using real-world data is that we learn [when we] extend findings from clinical trials [how they] actually apply to patients who may come from different socioeconomic backgrounds, who may come from different racial or ethnic groups, and who certainly may be less healthy than other patients. As a physician, I strongly advocate for the inclusion of patients from all those groups in clinical trials. I think it's a real disservice that they tend not to be included, and a lot of folks, thankfully, are working on that problem—I want them to continue that work. But in the meantime, there are lessons we can learn about the applicability of clinical trial findings to patients who may fall into underrepresented groups in the clinical trial world.

***EBO:* Do you have an idea yet how new end points or regulatory benchmarks may be incorporated as RWE becomes part of the decision process?**

Norden: There's a lot of discussion about this issue.… What should the end points in a real-world evidence-based analysis be? The truth is, the field is new enough that I don't think there's a definitive answer to this question. COTA and a number of other entities that work on real-world data and evidence generation from that data have been engaged collaboratively in a project put together by Friends of Cancer Research. We published a white paper online last year[9] in which we begin to address this question: Which end points that are derived from real-world data are predictive of end points that are derived from clinical trials? I think that this is a challenging area, because the methods that are used for end point determination are not well standardized, and there is some controversy about the extent to which these end points are predictive of overall survival or other clinical trial-based end points.

One thing that was heartening to see with the Friends of Cancer Research, is that 6 or 7 partners generated real-world evidence end points in different ways, but we actually came to the same answers. And we found there was a very high correlation between progression-free survival assessed using real-world data and overall survival, which is, of course, a critically important end point in cancer research.

So, there's encouraging preliminary evidence that suggests that real world–based end points like progression-free survival, time to treatment progression, time to treatment discontinuation… are correlated with clinical trials–based end points and with overall survival.

But I think we need more time to become confident about the situations where real-world end points may serve as adequate surrogates and where we must rely on clinical trials to get bias-free results.

***EBO:* What are some potential pitfalls or risks for health systems as they embark on the use of real-world evidence?**

Norden: I do think there are some risks for potential users. To give you a sense of what some of those are, I think one of the best described is the risk of bias when interpreting real world data.

Let's say we want to do a study based on real-world data, where we're comparing patients who have been treated with drug A or drug B. The problem is that the doctors who prescribed drug A versus drug B probably have reasons for making those choices. And those reasons, critics fear, may not be well captured in the data sets we are using to assess these questions. That's a real issue and one that must be addressed.

I think one of the potential ways to address it—and the approach COTA takes—is to generate a very clinically granular data set. That means we extract from the EMRs all the key prognostic variables that we know might drive differential outcomes and account for those in our analyses, using propensity scores or other statistical methods.

Now, the naysayer might argue that there are probably unmeasured variables that we can't extract from EMR data. I think that's true. No one should deny that reality—that is a limitation of real-world data. And that's why we have to be careful about how we apply this. The effect size we look for in real-world data maybe needs to be bigger than the effect size that would be persuasive if it was drawn from a randomized clinical trial.

The other issue one has to watch out for is that the quality of the data varies by provider and by source. Some sources are simply not well designed to answer certain questions. EMR data provides a certain level of clinical granularity, but on the other hand, if the patient leaves the provider on the EMR where you're tracking, then you may lose important pieces of information. That can be addressed with claims data, but claims data lack clinical granularity and only talk to you about healthcare transactions.

The advice I would give a potential user is to be really cautious and judicious. Whoever is producing the data [must do it] in an auditable, reproducible, high-quality way, where you have a trail of data from start to finish. [Make sure] you're not asking the data to answer questions that can't be satisfactorily addressed. We don't need to start by trying to replace clinical trials. We can start by saying, "How do learnings from real-world, evidence-based sources extend our understanding of clinical trials?'" ◆

"In COTA's view, one of the key advantages to using real-world data is that we learn [when we] extend findings from clinical trials [how they] actually apply to patients who may come from different socioeconomic backgrounds, different ethnic or racial or ethnic groups, and who certainly may be less healthy than other patients."

—Andrew Norden, MD, MPH, MBA

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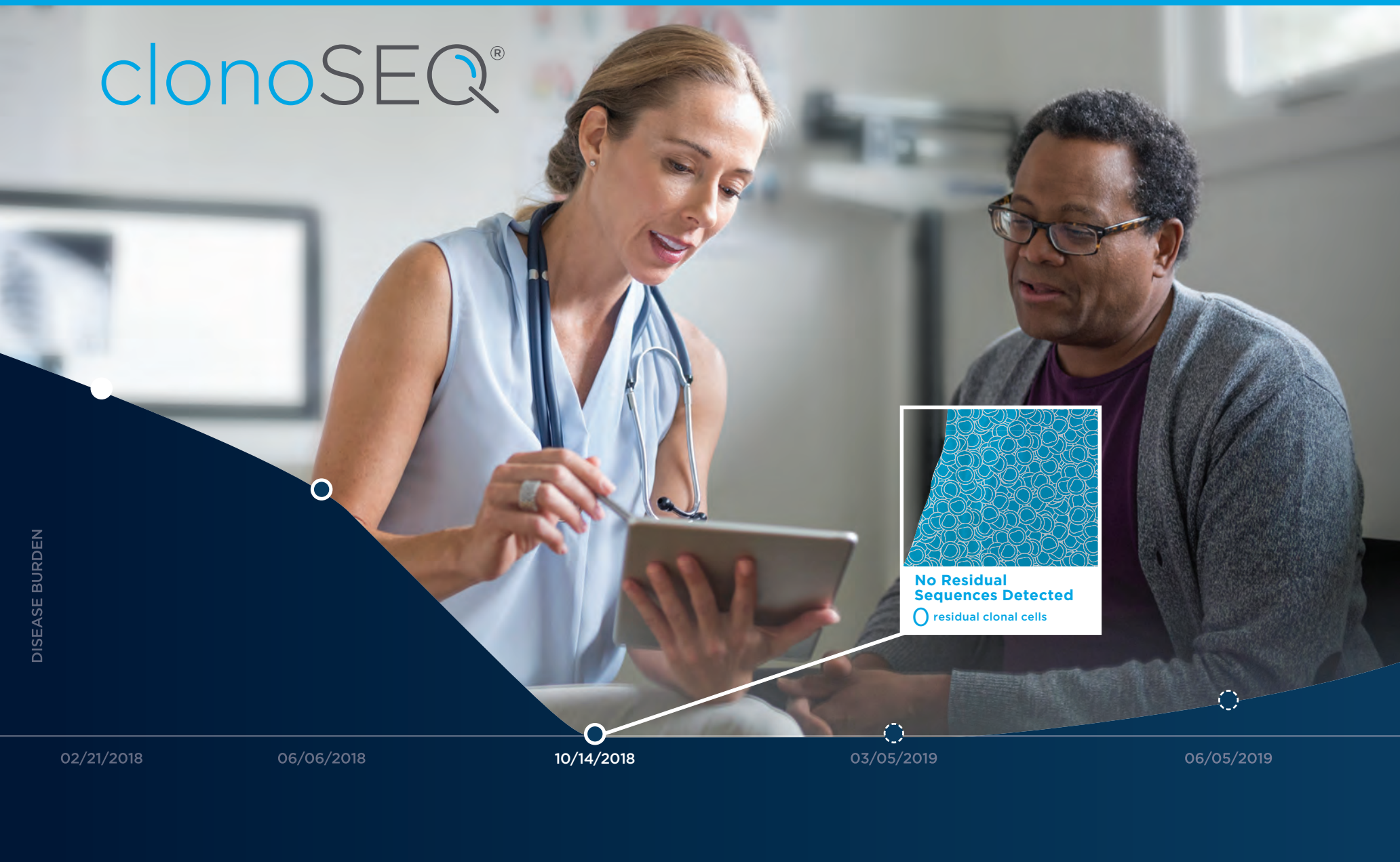

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Genetic Testing Can Reduce Suffering and Save Lives

Lauren Corduck

CORDUCK
Lauren Corduck is the founder and exeuctive director of Oneinforty.

I AM ONEINFORTY. In late 2016 at the age of 45, I sought genetic counseling and screening after a friend's urging. The screening showed I had inherited a *BRCA* gene mutation, putting my lifetime risk of developing breast cancer between 50% and 80%[1] and my lifetime risk of developing ovarian cancer (for which there is limited screening) between 40% and 60%.[2]

I was advised to have my fallopian tubes and ovaries removed—relatively easy same-day surgery that would have dramatically reduced my risk of developing ovarian cancer. But it was too late. Around the same time, I had magnetic resonance imaging (MRI) to determine the cause of severe back pain I had been experiencing for weeks. The MRI revealed an incidental finding of what turned out to be stage IV ovarian cancer. Given my family history of breast cancer on my father's side, coupled with my Ashkenazi (ie, Eastern European) Jewish heritage, my father and I should have been referred to genetic counselors and offered screening for *BRCA* gene mutations many years ago.

While undergoing my first course of treatment, I discovered that most people with Ashkenazi Jewish heritage are unaware that their risk of inheriting a *BRCA* gene mutation is 1:40, which is 10 times higher than that of the general population.[3] *BRCA* gene mutations put people at heightened risk of cancers including male/female breast cancer, ovarian cancer, and prostate cancer. If you know you are *BRCA* positive, you can often reduce your risk of developing a *BRCA* cancer or detect it early through enhanced screening, risk-reducing surgery, and/or chemoprevention. I founded Oneinforty (www.oneinforty.org), a Massachusetts-based nonprofit organization,[4] with a mission to prevent what happened to me and my family from happening to anyone else.

Oneinforty has learned that, surprisingly, most primary care physicians (PCPs) are not aware of the 1:40 risk of a *BRCA* mutation faced by their patients who have at least 1 Ashkenazi Jewish grandparent. Because of this lack of awareness, physicians do not routinely offer our high-risk population genetic counseling and screening. Consequently, most *BRCA*-positive men and women learn that they have a *BRCA* gene mutation only after receiving an advanced-stage cancer diagnosis and/or losing loved ones to the *BRCA* cancers. Compounding the problem is the fact that many PCPs are not familiar with nuances of BRCA such as:

- Half of people with a *BRCA* gene mutation have no known family history of the associated cancers.
- Men are as likely as women to both inherit and pass on *BRCA* gene mutations to their sons and daughters.
- Just 1 parent need be *BRCA* positive for each of a couple's sons and daughters to have a 50% chance of being *BRCA* positive.

Oneinforty is working tirelessly to educate PCPs and influence national healthcare policy and practice reform to increase the prevention and detection of *BRCA* cancer.

A genetic counselor who serves on Oneinforty's medical advisory board recently prepared a literature review for us containing some of the myriad seminal studies that support population-based screening for patients with Ashkenazi Jewish heritage. These include as follows:

1. ***Gabai-Kapar et al; 2014.*** The authors concluded that population-based screening would identify many carriers who are not evaluated by genetic testing based on family history criteria.[5]
2. ***Manchanda et al; 2015.*** Using a decision analytic model, the investigators showed that population-based screening would save more lives than family history-based screening; the lifetime cost savings would be £3.7 million ($4.61 million). Population-based screening would likely result in even higher lifetime savings today, because the cost of *BRCA* gene mutation testing has fallen considerably in the past several years.[6]
3. ***Manchanda et al; 2017.*** Findings support population-based testing for women who have 1 to 4 Ashkenazi Jewish grandparents.[7]
4. ***Lieberman et al; 2017.*** This qualitative study assessed a streamlined process that offered written pre-test information only, followed by genetic testing, with access to post-test genetic counseling. This process was viewed favorably by most individuals, suggesting a novel way to reduce barriers and expand access.[8]
5. ***Lieberman et al; 2018.*** Results showed that universal screening circumvents dependence on family disclosure, which at best is typically no higher than 50% for close relatives and significantly lower for more extended relatives who may still be at increased risk.[9]

Landmark studies such as those have shown that—compared with family history–based screening—population-based screening results in no lasting, undue psychiatric harm and:

- Makes economic sense
- Gives families agency over their own health
- Reduces *BRCA* cancer diagnoses
- Saves more lives

Since Oneinforty's launch 2 years ago, the organization has accomplished far more than I could have imagined.

- Through our efforts, we have reached more than 700 people with lifesaving information presented by panelists representing medical institutions, genetic counselors, mental health professionals, and "I am Oneinforty" storytellers.
- Feedback from our symposia has been universally positive, including comments such as "Very moving and thought-provoking" and "great mix of medical, clinical, and personal

speakers." Data show attendees' increased knowledge and intention to take action based on information presented.

- Through our new Medical Education Program, we have educated nearly 100 physicians at Massachusetts General Hospital and Newton-Wellesley Hospital about the 1:40 *BRCA*-positive risk faced by families with Ashkenazi Jewish heritage.
- Establishment of the Prevent Hereditary Cancer Coalition has brought together a diverse group of organizations and individual leaders from around the world committed to healthcare policy and practice reform related to the prevention of hereditary cancer.
- Backed by evidence-based research, we presented at the National Comprehensive Cancer Network (NCCN) Patient Advocacy Summit last December, requesting an expansion of national clinical practice guidelines to include routine screening for the *BRCA* founder gene mutations of men and women with at least 1 Ashkenazi Jewish grandparent, regardless of known family history. Our request was formally presented to NCCN's Genetic/Familial High-Risk Assessment: Breast and Ovarian Cancer panel earlier this year and is under review.
- Media outreach about Oneinforty's important mission and messages has reached tens of thousands through coverage by media outlets such as the *The Boston Globe, The New York Times, The Times of Israel, The Jewish Advocate, Shalom Magazine,* and WCVB-TV (Boston, Massachusetts).
- The Oneinforty.org website and *BRCAlert* e-newsletter provide resources and information of benefit to families at risk of hereditary cancer syndrome.

Patients with Ashkenazi Jewish ancestry are at least 10 times more likely than the general population to be *BRCA*-positive. It is not standard of care to identify this high-risk population."

In December 2017, I had a recurrence of the ovarian cancer and received a second course of chemotherapy. This past January, while driving with our 4-year-old son, I had a seizure caused by a brain tumor that turned out to be metastasized ovarian cancer. Fortunately, before losing consciousness, I pulled off the highway and asked a Good Samaritan to call 911. I had a successful craniotomy followed by radiation to my brain. I currently have a handful of malignant lymph nodes in my abdomen and pelvis and am on a poly ADP ribose polymerase (PARP) inhibitor, a breakthrough targeted therapy designed to treat and delay recurrence. Epilepsy and a blood-clotting disorder, both recent unexpected diagnoses stemming from the ovarian cancer, have made my medical situation and life far more complex and challenging.

Building Oneinforty has been the best "medicine" for me and my loved ones. We regularly hear from men and women who have learned of their hereditary cancer risk from Oneinforty and decided to get screened for the *BRCA* gene mutations. Most are 39:40 and relieved to find out that they are *BRCA* negative. Of course, some of these individuals such as these discovered that hereditary cancer syndrome runs in their family:

> *My mom has a* BRCA *gene mutation and is an ovarian cancer survivor. With guidance and support from Oneinforty, I found out that I too am* BRCA *positive. I'm glad to have this information and to begin my journey of informed medical decision making to reduce my risk of developing breast and ovarian cancer. I'm also grateful to be able to help my school-age son and daughter face their* BRCA *risk when they grow up.*
>
> *If it weren't for Oneinforty, I wouldn't have sought genetic counseling and testing and discovered that I have a genetic mutation that puts me at increased risk for colorectal cancer. My first colonoscopy revealed a very large polyp that contained precancerous cells. Now I have regular colonoscopies and am in a position to educate my sons, siblings, and parents about their hereditary cancer risk.*
>
> *Would you touch base with my wife? She may be* BRCA *positive. We just heard yesterday. Really might not have been tested if not for your talk! Obviously, we are still processing. We have not told anyone, including our 2 daughters who are 20 and 22.*

These Oneinforty constituents are grateful for the opportunity to make action plans with their physicians to manage their cancer risk and inform family members who may be affected. We remind *BRCA*-positive individuals who are overwhelmed by the diagnosis that they were *BRCA* positive since birth and that knowledge typically proves empowering.

George Washington University's Milken Institute of Public Health says on its website:

> *Understanding the difference between health* equality *and health* equity *is important to public health to ensure that resources are directed appropriately—as well as supporting the ongoing process of meeting people where they are.…For these reasons, providing the same type and number of resources to all is not enough. In order to reduce the health disparities gap, the underlying issues and individual needs of underserved and vulnerable populations must be effectively addressed.*[10]

There is clearly a gross *inequality* here: Patients with Ashkenazi Jewish ancestry are at least 10 times more likely than members of the general population to be *BRCA* positive. Oneinforty is illuminating a related and glaring healthcare *inequity*—namely, it is not standard of care to identify members of this high-risk population; inform them of their risk; educate them about managing their risk; and offer them ready, affordable access to emotional support, genetic counseling, and *BRCA* screening.

Oneinforty advocates for all families in which a *BRCA* gene mutation is lurking. We are Oneinforty, and we need the US healthcare system to meet us where we are: largely uninformed, underserved, grief-stricken, and anxious to face our high risk of having hereditary cancer syndrome. We should routinely be given the opportunity to find out our *BRCA* status before cancer strikes. From personal experience, I know that—as scary as the risk of having a *BRCA* gene mutation may feel—hearing the words "You have cancer" is far more devastating and life altering. ◆

AUTHOR INFORMATION

Lauren Corduck is the founder and executive director of Oneinforty.

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How Data, AI Are Unlocking Secrets to Better, More Efficient Cancer Care

Allison Inserro

PRACTICES TAKING PART in the Oncology Care Model (OCM) will soon reach a point when 2-sided risk will be forced upon them,[1] and innovation will be key to survival, according to a group of stakeholders who recently discussed their successes and challenges.

Innovation will hold the key to improving quality metrics, patient care, and the bottom line, healthcare executives said at a July 18, 2019, meeting of the Institute for Value Based Medicine®, a special project of *The American Journal of Managed Care®*.


SHAPIRA

Iuliana Shapira, MD, chief medical officer of Regional Cancer Care Associates (RCCA), served as moderator and host for the meeting held in Teaneck, New Jersey, where panelists shared how they are transforming piles of data into action items that can improve health and quality of life. Driving this transformation are new analytic tools and artificial intelligence (AI).

Barry Russo, chief executive officer of The Center for Cancer and Blood Disorders (CCBD), based in Fort Worth, Texas, described the journey the oncology practice has been on since it began working with Jvion, a prescriptive analytics company, to help it better manage the 6000 patients it sees a year.


RUSSO

Russo said there are 5 areas where AI can be particularly valuable:

- Coping with a data explosion, in which medical data are projected to double every 73 days by 2020.[2]
- Addressing physician shortages and rising burnout
- Taming an increased number of medical images
- Managing vulnerable populations
- Dealing with increased costs and complexity in the life sciences

CCBD went through several phases as the practice worked to figure out how to best use AI, Russo said. At the point of care, physicians are using it to risk-stratify patients.

"When I went through the litany of how many value-based arrangements we have, that equates to about 1000 to 1100 patients that we should be managing at any given time, meaning that they need case management oversight," said Russo.

However, he noted that CCBD "can't hire enough case managers to focus on all of the bodies we're bringing into a value-based arrangement. It's not possible, financially or even or from a people standpoint."

In trying to determine which patients needed active management, the practice started with all patients who were in stage IV, which ended up being the incorrect move, he said. That group did not have higher costs than others. Then the practice looked at all the patients who had cancer of the lung, head and neck tumors, and pancreatic cancer, as well as those who were stage III and beyond. That group, too, was not focused enough.

CCBD realized that by participating in the OCM, they had 6 years' worth of claims data, because practices in the OCM are responsible for the total costs of care, not just oncology costs.[3] It turned out their most costly patients are cancer survivors—those who are 5 to 10 years post treatment who are still being monitored.

"They are kind of healthy," said Russo, "except they fall. They have joint replacements. They have MIs [myocardial infarctions], and when we looked at our data, we're like, wait a minute. We have people who are just on AI; unfortunately, they're attributed to us because we see them for E&M [evaluation and management] visits more often than anybody else does. And they're costing us a fortune."

THE LESSONS FROM JVION

Jvion ingested all of CCBD's clinical data and mixed it with socioeconomic and other data to create a proprietary system of 7 vectors. The organization found that socioeconomic data is a huge flag that signals risk for more complex care in a patient population. Risk factors include having lower education levels, lower income, living alone, and residential instability, or not owning a home.

Data companies like Jvion buy zip code–level data from government agencies, whether it is the Census Bureau or the Department of Housing and Urban Development, or from technology companies like Amazon, which signals a person's level of technology literacy.

"It isn't just clinical complexity, it's socioeconomic complexity and how you link the 2 of them together," Russo said.

Jvion sorts patients into 7 vectors at risk for the following:

- 30-day mortality
- 30-day pain management
- 6-month depression risk
- 6-month risk for deterioration
- 30-day avoidable admission
- 30-day emergency department visit
- 90-day readmission

It also takes in historical claims data from every other provider.

CCBD soon started sending reports back to physicians based on their individual data. Some resisted the information, but others were open to the idea, Russo said. The reports offered value because they flagged which patients would never have been identified as being at risk of morbidity or mortality.


PORRETTA

CCBD is also validating the 7 vectors internally, with varying levels of progress. For instance, the 30-day mortality risk is 35% validated, while the risk of a patient becoming an inpatient admission within 30 days is 100% validated.

Case managers can now focus on the people at the highest risk, Russo said. CCBD is still optimizing how Jvion can recommend interventions, but one thing it can do is automatically refer patients for pain management. In addition, the psychology team is proactively calling patients flagged by the system, which the practice now calls "the brain."

Jvion also is using the system to identify patients who show up in multiple vectors, as Russo said, because "people that are at risk for more than 3 [vectors], maybe that actually would be a better way to catch the patients."

CCBD is also identifying their own group of what Russo calls "socially challenged" patients so that social workers can make proactive calls to this group. The social workers make sure that applications for financial assistance are filed; Russo noted that the more people that file and are approved for help, the more the OCM score rises.

Another outcome: As a result of the ability to look more closely at data related to morbidity and mortality, referrals for pain management, palliative care, and hospice have all climbed.

In addition, CCBD is asking for Jvion to create a vector for inpatient fall risk; in the meantime, CCBD asks patients if they have had a fall in the past 30 days. Russo said they are "begging Jvion to move into the outpatient area, so that we can get those patients automatically referred to our pre-hab program." This is because rehab costs are higher than those for inpatient admissions and are attributable to CCBD under the OCM.

Without AI, "there's no way to manage these populations. We've got to have a better way," said Russo.

The next steps for CCBD will be to use AI to go after issues related to electronic health records (EHRs) so that clinical, financial, molecular, pathways, costs of care, referral preferences, or

requirements of accountable care organizations data are integrated and can be more than just a repository that cannot be acted upon.

The biggest issue, however, is putting all of the relevant information about a patient before the provider at the point of care, without the EHR rejecting requests and creating more work, Russo said. As an example, he pointed to UnitedHealthcare's decision to only pay for the brand-name pegfilgrastim, Amgen's Neulasta, and not a biosimilar as of July 1. Russo noted that Aetna uses Sandoz's Zarxio, and other payers may insist on something else. As more oncology biosimilars enter the marketplace, this will only become more complicated for physicians as they try to enter orders, he said.

"We have to go back to the physician, start the order process again, and go back to the precert process again. We don't have time for it. You can't do it. Biosimilars are complicating the whole process of the point of care so much," he said.

USING DATA TO ENGAGE WITH EMPLOYERS, DRIVE VOLUME

When the physicians at Michiana Hematology Oncology in South Bend, Indiana, decided to get ahead of what they saw as a dawning technological transformation in healthcare, they wanted to do so on their own. Kim Woofter, RN, who works at the practice, began using a local data analytics firm a few years ago to understand all of their disparate data sets so physicians could start acting on them.


WOOFTER

Then South Bend awarded a $1-million grant to build their "data lake." With that, Michiana spun that part off into a new company, the Advanced Center for Cancer Care (ACCC), which is now the data component of Michiana, said Woofter, who is now the executive vice president of strategic alliances and practice innovation at ACCC.

Michiana Hematology Oncology, a practice with 15 physicians, 9 locations, and about 4000 new patients a year, intended to use the data for its own internal purposes. But then a manufacturing firm with about 8500 employees called her and asked, "Hey, Kim, if you can look at your data, can you look at *my* spend data?"

While employers across the country are struggling with healthcare costs, this company was also trying to retain a skilled workforce in an area where the unemployment rate was 1.2%; their goal was to lower their costs so that they could also drastically reduce the workers' share.

The data lake now includes data sets from oncology, employers, orthopedics, surgery centers, and multispecialty groups. The most important thing, Woofter discovered, was being totally transparent in the cost of care; she said she was shocked by the variances in payments between what self-insured employers (even her own company) paid to the network and what the network paid providers. It gave her a chance to see "both sides of the coin," she said.

To really make a difference with employers and demonstrate value, she recommends setting up a fee schedule that bills the contracted rate. In one case, she was able to show that for a single ill employee, the employer was charged $4400 for Neulasta even though the local hospital charged $19,519.

Co-pays change patterns as well, Woofter said; for example, at an outpatient center, for infusion, the copay is zero, but at a hospital, it's $500.

"Those HR directors truly believed in their very soul that they had no control at all over the cost of healthcare that they were paying," Woofter said. "We all agree that quality is the No. 1 denominator, but we have to marry that up with costs if we're going to be a good steward."

Another step they took was to create an app that showed the doctors the cost of the treatments they were prescribing. They are also trying to create what she called "a meaningful fee schedule" that will be community wide. And employers are getting "trigger alerts" if certain high-cost patients are pushing them closer and closer to the stop-loss limit (the employees are not named).

Employers are also interested in looking at predictive analytics in order to keep more people healthy and working so that they don't have to go through the recruitment process again.

"We believe that our strategy was to solve the problem of the employer, instead of going in to say, 'Here's how much I want from you today'," Woofter said. "We took the strategy of, 'I'm here to solve your problem. And I want to be your partner.'"

VALUE IN THE EYES OF A PROVIDER AND PAYER: HORIZON AND RCCA

Shapira, who became RCCA's chief medical officer in March 2019,[4] explained that RCCA is a large OCM practice that operates in Connecticut, Maryland, New Jersey, and Washington, DC.

Lani Alison, BSN, MS-HCQ, PCMH, CCE, RCCA's vice president of clinical affairs, noted that the organization takes the OCM's 6 practice redesign activities and applies them to all patients, regardless of payer. "The OCM actually set the standard for us because we believe that is the highest and toughest standard of care," said Alison.


ALISON

There are different definitions of quality and value, but she noted, "quality becomes very personal to people with cancer."

"For us, we would like to deliver on patient value," she said

Similar to CCBD, RCCA uses a population health model and applies it to oncology to stratify patients, from low to high risk.

Both Alison and Susan Porretta, RN, BS, FAHM, the director of partner transformation at Horizon Blue Cross Blue Shield of New Jersey, the state's largest insurer with 3.8 million customers, both said they are trying to improve palliative care and how doctors discuss dying. They urge that these conversations not take place at the last minute, when it becomes more difficult.

RCCA began adding licensed clinical social workers 2 years ago, a move physicians initially resisted. But now they want more social workers, Alison said.

Horizon also began a pilot palliative care project a year ago and may expand it to pediatrics, Porretta said. "If you were a physician who graduated from medical school more than 10 years ago. you were not educated on advanced care planning," she said.

During a panel discussion that followed the presentations, Terrill Jordan, JD, RCCA's president and chief executive officer, asked Russo and Woofter if they have "been able to convince your physicians that the data or AI will actually reduce their workload so that they're not working as hard, because it will inform their decision making—inform how they deal with patients?"

Woofter said her organization is starting out small and is not quite up to using AI yet. Her hope, she said, is that technology will advance to a point where she could say to a potential hire, "You don't have to document. You just come here and be a great doctor."

"Is it the reluctance to accept change? Or is it the fact that they feel that the pathway [imposes] onto their practice?" asked Shapira.

"It's the latter. It's probably a little bit a little both," said Russo. "Doctors are afraid it will create more work if they have to click through more screens or boxes."

One audience member asked how the role of the caregiver is represented or changing in the OCM. Alison noted that one of her best friends died from stage IV glioblastoma, and the institution where her friend was treated took extremely good care of her friend's surviving son. Discussing her father's own, current cancer fight, she said, "Caregivers really are the hidden keys to getting to the patient."

"They already see that they need to talk to me, because whenever the hard questions are being asked of my father, he looks at me."

"You have to meet the caregiver at the first hello," she tells her staff. ◆

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Understanding the Role of the OB/GYN in Evaluating Hereditary Cancer Risk

A Conversation With Barbara S. Levy, MD, Vice President, Health Policy, American College of Obstetricians and Gynecologists

Mary Caffrey

A WOMAN WHO RECEIVES a diagnosis of breast or ovarian cancer or learns she faces an increased cancer risk because of a relative's diagnosis may have many conversations with healthcare providers about her options. But before she consults with a genetic counselor, medical oncologist, or surgeon, her decision-making process likely starts with a healthcare provider she already knows: her obstetrician-gynecologist (OB/GYN).

BARBARA S. LEVY, MD

The news about breast cancer may have come after a mammogram her OB/GYN ordered during an annual visit. A diagnosis of ovarian cancer may have arisen after sudden weight gain, bloating, or midmonth bleeding prompted a visit to the OB/GYN. Thus, the perspective of the OB/GYN, who is the primary point of care for many women, matters greatly in any discussion of prevention and treatment of hereditary cancers.

To gain that perspective, *Evidence-Based Oncology*™ spoke with Barbara S. Levy, MD, vice president of health policy for the American College of Obstetricians and Gynecologists (ACOG), which represents 58,000 OB/GYNs and women's healthcare professionals. Levy administers ACOG's Office of Global Women's Health programs, which focus on improving patient safety and healthcare quality worldwide. She oversees a variety of programs that promote innovation, safety, quality of care, health economics, and health information technology and clinical informatics.

In the reimbursement area, Levy has served on the American Medical Association/Specialty Society Relative Value Scale Update Committee since 1999 and chaired for 2 consecutive terms. The committee is a volunteer panel of physicians and providers that advises CMS on what it costs to perform certain medical services and pay practice expenses.

ACOG's position statement, the Committee Opinion on Hereditary Cancer Syndromes and Risk Assessment, was first published in June 2015 and reaffirmed in 2017.[1] Its chief recommendations are as follows:

1. A hereditary cancer risk assessment should be performed to identify patients and families at risk of developing certain cancers, and ob-gyns should provide this assessment or other providers and be updated regularly.
2. If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a cancer genetics specialist is recommended to gather family history, assess risk, and provide counseling, which may lead to genetic testing.

Below is an edited version of a conversation with Levy on ACOG's positions on risk assessment of hereditary cancers, current trends in genetic testing, healthcare usage, prior authorization, and reimbursement from the perspective of the obstetrician-gynecologist.

***Evidence-Based Oncology*™ (*EBO*): At this year's annual meeting, the National Comprehensive Cancer Network (NCCN) noted that its guidelines for genetic testing do not align with those of the American Society Breast Surgeons (ASBS) and might merit more examination. ASBS called for making testing available to all patients with breast cancer and some without who meet NCCN guidelines.[2]) Where does ACOG stand?**

Levy: We take care of women at the primary point of care, and we are very focused on the general population—we are focused on what is appropriate in shared decision making and on the need to give our members the education and support they need. This means staying up-to-date on options for screening, what a positive screen might mean, and what the follow-up options are.

There are differences in focus for each organization. If your organization treats breast cancer, you're focused on capturing every case of breast cancer. If you're an OB/GYN, you want that balance for your patient. Overuse of testing can create fear and anxiety, so you want to help your patient understand what is best for her unique circumstances. For a woman with a very high risk [of cancer], that means counseling for her and her family. For women with average and low risk, as their primary care point, we help them understand what their own values are, and people are coming in with vastly different values. Some want to know everything; some are so highly anxious that they can't know everything—they don't want to have their anxiety raised by the uncertainty, and they would rather not be tested.

I think it's a difference in perspective—for us, it's the marriage of public health with individualized and personalized healthcare. When you are an ob-gyn, you are taking care of a large population with individualized needs. Part of our training is in public health, which is delivering the greatest good for the public. [There's no value] in a genetic test to uncover a heart condition in someone who is 85, but there is for a genetic test that reveals a high risk of someone developing breast cancer when they are in their 30s, so they can live a totally normal life span. These are the kinds of things our organization would look at somewhat differently than a cancer organization.

***EBO:* Several years ago, insurers including Cigna called for women to not receive hereditary testing unless they receive guidance from a genetic counselor.[3] There has been discussion that there are not enough genetic counselors to meet demand. Where does ACOG stand on this issue?**

Levy: ACOG feels pretty strongly that OB/GYNs are well trained to do genetics counseling. We are not PhDs in genetics counseling, and there are compelling circumstances to recommend a referral. But there are not enough genetic counselors for every family and to evaluate every woman for hereditary cancer syndrome. There are some online resources [for counseling via telehealth], but we feel strongly that establishing a relationship with the person is important for shared decision making—some connection between the provider and the patient and her family is important to understanding a patient's values. That isn't necessarily going to be possible in the first visit with an online provider. We feel the ob-gyns are well positioned to help patients and families make these kinds of decisions.

***EBO:* In 2013, following her mother's death from ovarian cancer, Angelina Jolie revealed that she had received a double mastectomy because she carried a *BRCA1* mutation.[4] There was a surge of interest in genetic testing, along with reports about overtesting and overutilization of healthcare services. Where do things stand now in terms of testing? Is there too much, too little, or the right amount?**

Levy: It's settled down. Whenever there is a celebrity out there, whether it's an antivaxxer or a person with a hereditary cancer, it makes everybody afraid. People do go in, and they want testing. For people who could afford it, there was overtesting—they would pay for it, even if they didn't meet the guidelines. If they meet the guidelines and they have coverage, they are screened with the right screening tool.

We are trying to find that sweet spot between too much and too little for the appropriate patient. It bothers us all at ACOG that women without coverage will use over-the-counter [also called direct-to-consumer] genetic testing, thinking that's a reasonable and adequate test, when the quality is quite different from a medical-grade test. With the *BRCA* mutations, there are many variants of that gene that the over-the-counter test will miss; the medical-grade version will test for 100 variants. Doing an over-the-counter test is not the same.

EBO: **At this year's meeting of the American Society of Clinical Oncology, findings presented showed that increased coverage has helped close gaps in cancer care.[5] What is ACOG's view? Does the organization see disparities in testing and/or in follow-up after a positive result?**

Levy: There are a couple of issues here, involving both access and coverage. If a woman has very simple, bare-bones coverage, it might cover cancer screening but not the treatment [if cancer is discovered]. There might be a reduction in disparities in screening, but there are problems if follow-up is delayed, [especially] if there are already issues of trust in the medical system—if you come from a place where there's been experimentation or abuse of the population in particular. [Examples include families affected by the Tuskegee syphilis study[6] or those subjected to forced sterilizations by the Eugenics Board of North Carolina.[7]]

But people in general may find it difficult to trust that their information is safe and that it will not affect their future ability to get insurance to a job. We hear about data breaches in health insurance, so there is a lack of trust among some people about their data.

I think access to coverage is a huge issue that helps reduce disparities in shared decision making. At ACOG, we make it clear that our members should be advising women about the hazards of some of this information and how it can be used. We advocate strongly for laws and rules that prevent employers and insurers from using information to restrict people from jobs or restrict coverage. There's also a lot of policy that has to go behind creating a safety structure for this data.

EBO: **What is the situation in states where Medicaid expansion has not taken place?**

Levy: Here, we are more focused on obstetrical care. It's basically the same issue—in states without Medicaid expansion, women are disproportionally affected by lack of coverage. It affects care for mental illness, obstetrical care, substance abuse—it's across the board—including preventive medicine and public health. We're trying to make sure there are proper public health interventions, but we are looking at widening disparities between states that have expanded Medicaid and those that have not.

EBO: **The trend across guidelines has been toward recommending more genetic testing, not less. However, we continue to hear reports of challenges with reimbursement. What do your members report?**

Levy: We hear about the burdens with prior authorization. Getting a test covered is a huge issue for all practices with all the hoops that the payers put in the way to decrease utilization. Cigna has a requirement that all genetic counseling must be done by a certified genetic counselor. With several companies, we've been trying to talk to the insurers to show them that among provider groups, the OB/GYN has the right background to counsel people. So, from our perspective, the biggest burden is prior authorization.

When it comes to the cost of the test, the reimbursement goes to the laboratory—it doesn't go to the OB/GYN. Sometimes there is an administrative burden if the lab does a different test and the patient gets a bill for $3000. We don't get paid to do the tests; we get paid to do the counseling and the management.

EBO: **What are some other challenges you see?**

Levy: Cancer screening and genetic screening are complex. There are all kinds of tests, and labs want to take those [mutations] that are well known and add a hundred more to the test. We end up with more mutations of unknown significance. There are games being played on all sides, and patients and providers are kind of stuck in the middle. [In June, the HHS Office of Inspector General issued a consumer fraud alert.[8]]

We recognize that with precision medicine, screening will change for families that have a predisposition to a disease. For colorectal, ovarian, or breast cancer—for those cancers where the hereditary predisposition is well established—it's easier. But the labs want to expand testing, and keeping them in check is a little bit challenging.

With the changing landscape, our goal at ACOG is help our OB/GYNs and patients get the best possible information for shared decision making. None of these decisions are straightforward, rubber-stamped kinds of things. We think OB-GYNs can provide the best service to our patients. ◆

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FILM REVIEW

Jim Allison: Breakthrough Traces the Unexpected Creative Paths of a Scientist and Immuno-Oncology

Mary Caffrey

ALBERT EINSTEIN SAID, "The great scientists are artists as well."[1] Leonardo da Vinci painted *The Last Supper* and was the first to define atherosclerosis.[2] Louis Pasteur's love of art informed key theories on the shapes of crystals.[3] Pure innovators transcend the lines between art and science, their creativity fuels the leaps forward, and their technical mastery brings ideas to life.

Such is the story of James P. Allison, PhD, the Texas immunologist who conceived during graduate school that T cells could have a role in fighting cancer—and then chased this idea to develop checkpoint inhibitors, part of the immunotherapy arsenal now called the fourth pillar of cancer treatment, with radiation, surgery, and chemotherapy.[4]

ALLISON

By the time Allison won a share of the 2018 Nobel Prize for Physiology or Medicine, the honor came as no surprise.[5] But for years, this had been an end point few would have predicted from a gravely voiced, hard-partying outsider equally at home in the lab or onstage with his harmonica. This improbable journey now unfolds in *Jim Allison: Breakthrough*,[6] a documentary from director Bill Haney that offers a portrait of an unlikely hero who dismantle stereotypes about science and scientists.

Breakthrough premiered in March at South by Southwest and opens in select cities on September 27, before a nationwide release on October 4.[6] Haney spoke with *Evidence-Based Oncology*™ (*EBO*) about the film's mission and his time working with Allison, who won the Nobel Prize the morning after principal filming ended in New York City. The film concludes with a shot of Allison getting the call from Stockholm; his son, Robert, filmed it in the New York City hotel where Allison was staying with his wife, oncologist Padmanee Sharma, MD, PhD, during a conference.[7] Both are on the faculty at The University of Texas at MD Anderson Cancer Center. Allison is the Vivian L. Smith Distinguished Chair in of Immunology, director of the Parker Institute for Cancer Research, and the executive director of the Immunotherapy Platform; Sharma has a dual appointment as a professor in the Department of Genitourinary Medical Oncology and a professor in the Department of Immunology.

Haney hopes *Breakthrough* helps young people see scientists differently and to view them as creators in the same vein as actors or filmmakers. "In thinking about the creative landscape, we don't include the scientists in the way their spectacular contributions justify," he said in the interview.

He set out to make a film on the immunotherapy revolution, and based just on the science, all roads led to Allison. The Nobel Prize came 7 years after the FDA approval of ipilimumab (Yervoy) to treat metastatic melanoma. Although the drug did not work in every patient, in those who responded, it brought results never before seen in a disease diagnosed in more than 65,000 people a year; at that time, melanoma deaths exceeded 9000 a year and were rising.[8,9]

Then the director learned the tale of a boy from Alice, Texas. At age 11, Allison lost his mother to lymphoma. His grief-stricken father then abandoned him for stretches. In high school, his steadfastness that evolution was real got him the paddle and a boot from biology class. It became clear to Haney that "this was an extraordinary and unlikely hero."

The story of Allison the creator, Haney said, comes not just from his love of music and people "but from thinking differently, from imagining how the T cell works differently."

The film opens in Texas, where Allison grew up the youngest son of a family doctor and a beautiful mother who falls ill; Allison later learns it was cancer. His mother's loss caused such upheaval that the school district paired young Allison with a family to stay with when his father was traveling. Haney's curation of family photos and film snippets meant the South by Southwest premiere marked the first time Allison had seen footage of his mother carrying him lovingly as a toddler.

"There was a big hole, a lot of loneliness," Allison says in the film, surfacing the hurt that seems fresh some 6 decades gone. Cancer later claimed the lives of 2 uncles as he grew up, before he built the traveling assembly of students and colleagues who have shared his pursuit of a cure.

MUSIC, AND WOMEN, AS CHAMPIONS

Allison also filled the void with his harmonica; to this day, he plays with fellow immunologists in their band, the Checkpoints. Winning the Nobel Prize also brought perks like playing with a fellow Texan, singer-songwriter Willie Nelson, and the film details Allison's first encounter with Nelson at the dawn of the scientist's research career in a California bar. Music, merriment, and the balance of working hard and playing hard are themes of *Breakthrough*. Allison builds fierce loyalty that one former student likened to a "pirate ship" while giving his team and himself bouts of "nonlinear" thinking to push their creative limits.

"Science isn't the solitary life that most of us imagine it to be," Haney told *EBO*. "Science is a social act, as well, and Jim is very skilled at that.… All of us are able to work harder with people we enjoy than with people we don't enjoy."

The atmosphere fueled Allison's method of doing the *hard* experiments, the ones that work only if a theory is rock-solid, such as Allison's insistence that a paper[10] claiming the protein receptor CTLA-4 activated the immune response was incorrect. But it paid off on the fateful morning when Allison checked on mice given the antibody developed to shrink tumors based on the anti–CTLA-4 theory.[11]

The tumors were gone. Now came the quest to turn the antibody into a cure.

If the loss of his mother left "a big hole," the other women in Allison's life have been his champions. Allison's single-mindedness in getting the antibody that became ipilimumab approved took its toll, and during this period, he and his first wife, Malinda, separated after decades together. Malinda Allison is no longer Jim's wife, but she is essential to *Breakthrough*; Haney said Malinda attended the premiere, where the director appreciated the deep, mutual respect between the former spouses. (The credits feature special thanks for Malinda Allison's contributions.)

Midway through the film, Rachel Humphrey, MD, gives the pharmaceutical industry its warmest face ever when she describes leaving Bayer for Bristol-Myers Squibb (BMS), specifically to be the deep pocket behind the antibody Allison was developing with a small biotech company called Medarex.[12] Humphrey pulls no punches portraying the grief she endured after Pfizer canceled work on a competing immunotherapy, which signaled that the new drug class could be a failure.[13]

And Sharma is introduced in the film the way she met Allison—through the science. She ran an early clinical trial of ipilimumab, in which tumors quickly vanished for 3 of the 12 patients.[14] "You never see this," she says on-screen. "It's like the pot at the end of the rainbow."

FROM IMPOSSIBLE IDEA TO CURE

Ultimately, *Breakthrough* tells the story of science and how the best science is about breaking paradigms. Allison first learned about T cells as an undergraduate at The University of Texas shortly after they were discovered in 1959[15] and became fascinated with the idea that these soldiers of the immune system could someday fight the disease that had claimed his mother.

When the FDA's approval for ipilimumab came in 2011,[8] some 15 years had passed since Allison had proved that CTLA-4 acts as a brake on T cells.[11] A year later, while still at the University of California at Berkeley, he developed the monoclonal antibody that blocks CTLA-4, setting off the immune system to attack cancer.[16] By this time, almost 3 decades had passed since Allison had shown up from Smithville, Texas, at a 1982 conference with a poster that identified the T-cell antigen receptor—the

groundbreaking step that showed how T cells recognize invaders and upon which today's most breathtaking therapies are built.[17]

As fellow scientists discuss in *Breakthrough*, Allison faced skepticism not just for his own ideas but also about immuno-oncology itself, after almost a century's worth of attempts to turn the immune system against cancer had fallen short.[15,18] "Every time, it was met with disappointment," Tyler Jacks, PhD, director of the Koch Institute, who is interviewed in the film, says in a preview.[19]

But Allison's believers stayed true. Almost his entire lab followed him across the country from Berkeley to New York City when clinical trials for ipilimumab began at Memorial Sloan Kettering Cancer Center. Humphrey describes her own genetic predisposition to cancer and the family members she has lost. "The stakes are so high," she says through tears. "Somehow it just didn't matter when people yelled at me."

Allison still boils over, years after ipilimumab has saved lived and changed cancer care, when he talks about the delays. "I knew this was a way to cure cancer, and I'll be damned if I'm just going to let that lay around," he says, seizing up at the memory of the search for financing. "I need to get it into people. I need to get it into patients."

The urgency became personal. Allison's brother died of prostate cancer in 2005, and he was given a diagnosis of the same cancer a week later.

FROM RISK TO REWARD

For a time, Medarex and its chief executive officer, Donald Drakeman, were making more headlines with mice than with medicine. Papers across the country carried a March 2000 Associated Press story about Medarex's soaring stock price, which was based not on a drug it was developing but on its ability to make the immune systems of mice produce human antibodies.[20] Medarex had acquired the mouse technology along with a top scientist, Nils Lonberg, PhD, a few years prior, and Lonberg's arrival would prove key in the biotech's handshake deal to develop Allison's antibody.[21]

In the early 2000s, Medarex and Drakeman were biotech darlings, but for every fan, there were skeptics. The business section of my former newspaper, the *Times of Trenton*, dutifully published the quarter-by-quarter losses for the company, which was based in nearby Princeton, New Jersey. "Sales ballooned but falling licensing revenues caused losses to skyrocket last quarter and last year," began the March 19, 2003, article in which Drakeman warned, once again, that things would get worse before they got better.[22]

It turns out that financials of immuno-oncology matched the biology. *Breakthrough* does an outstanding job of explaining how Allison, fellow scientists, and BMS not only had to develop a drug that worked but also had to persuade the FDA to develop a new paradigm for approving a drug that worked *differently*. Harnessing the immune system to take up the fight, instead of killing cancer with poison, means tumors will grow before they shrink; thus, approval should be based on overall survival. This was a tough concept, even for very smart people.[23]

Which meant Allison couldn't be just a scientist. He had to be a pain in the rear. And he was.

Matt Richtel of the *New York Times* is more tactful in the film. "You don't know whether the new idea is something potent or deadly," he says. "It takes a really powerful idea combined with someone willing to push it forward to make it happen."

Skepticism followed ipilimumab at almost every step. On November 9, 2004, the day BMS announced it would invest $25 million with Medarex to develop the agent then known as MDX-010, BMS' shares fell, at that point down 17% on the year.[24] On May 7, 2008, a month after Pfizer's bombshell and weeks before the American Society of Clinical Oncology (ASCO) annual meeting, the FDA announced it wanted more data on ipilimumab. One analyst told reporters that ipilimumab's ASCO data would have to outperform the antibody Pfizer had just abandoned for ipilimumab to be commercially viable.[25] The witnesses in *Breakthrough* testify that BMS' decision to invest in more studies went against convention. BMS acquired Medarex not long after the FDA's initial thumbs-down; an analyst said this was likely, given what the press called "Medarex's string of drug failures."[25,26]

Allison knew better. Woven through *Breakthrough* is the story of metastatic melanoma patient Sharon Belvin, given a diagnosis and treated with chemotherapy days before her wedding at age 22. Ipilimumab's ability to make her tumors disappear told Sloan Kettering oncologist Jedd D. Wolchok, MD, PhD, that something big was happening. Belvin is now cancer free, and she and Allison each share the story of the day they met at the clinic in 2006.

"Until then it was just numbers; it was a concept," Allison says in the film. "She was the first patient.… Now she has a family, 2 beautiful kids.

"I still choke up when I think about that." ◆

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Rubraca® (rucaparib) tablets:

TWO INDICATIONS. MORE PATIENT TYPES.

RUBRACA MAY HELP YOUR DIVERSE MEMBER POPULATION:

for the **maintenance** treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and

for the **treatment** of adult patients with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca

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MAINTENANCE

Debra, 67

- *BRCA* wild-type
- Taking Rubraca to maintain response to most recent platinum-based chemotherapy

These individuals are not actual patients.

*In the ARIEL3 trial of Rubraca as maintenance therapy, investigator-assessed median progression-free survival (PFS) in the overall study population was 10.8 months in the treatment group versus 5.4 months in the placebo group (HR=0.36 [95% CI, 0.30, 0.45], *P*<0.0001).[1]

Study design: The efficacy of Rubraca for maintenance treatment was investigated in a randomized, placebo-controlled, double-blind, multicenter clinical trial of 564 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who had a response to platinum-based chemotherapy. The efficacy of Rubraca was evaluated in 3 prospectively defined molecular subgroups in a step-down manner: 1) *BRCA* mutation-positive patients, 2) patients with homologous recombination deficiency (HRD), and 3) all randomized patients.[1]

Select Important Safety Information

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) occur uncommonly in patients treated with Rubraca, and are potentially fatal adverse reactions. In approximately 1100 treated patients, MDS/AML occurred in 12 patients (1.1%), including those in long term follow-up. Of these, 5 occurred during treatment or during the 28 day safety follow-up (0.5%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 28 months. The cases were typical of secondary MDS/cancer therapy-related AML; in all cases, patients had received previous platinum-containing regimens and/or other DNA damaging agents.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1).

Monitor complete blood counts for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities (> 4 weeks), interrupt Rubraca or reduce dose (see Dosage and Administration (2.2) in full Prescribing Information) and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks or if MDS/AML is suspected, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Based on its mechanism of action and findings from animal studies, Rubraca can cause fetal harm when administered to a pregnant woman. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca.

Most common adverse reactions in ARIEL3 (≥ 20%; Grade 1-4) were nausea (76%), fatigue/asthenia (73%), abdominal pain/distention (46%), rash (43%), dysgeusia (40%), anemia (39%), AST/ALT elevation (38%),

CLOVIS ONCOLOGY

Reference: 1. Rubraca [package insert]. Boulder, CO: Clovis Oncology; 2018.

In a phase 3 study for maintenance treatment, Rubraca significantly extended progression-free survival versus placebo, **regardless of *BRCA* status**[1]*

constipation (37%), vomiting (37%), diarrhea (32%), thrombocytopenia (29%), nasopharyngitis/upper respiratory tract infection (29%), stomatitis (28%), decreased appetite (23%), and neutropenia (20%).

Most common laboratory abnormalities in ARIEL3 (≥ 25%; Grade 1-4) were increase in creatinine (98%), decrease in hemoglobin (88%), increase in cholesterol (84%), increase in alanine aminotransferase (ALT) (73%), increase in aspartate aminotransferase (AST) (61%), decrease in platelets (44%), decrease in leukocytes (44%), decrease in neutrophils (38%), increase in alkaline phosphatase (37%), and decrease in lymphocytes (29%).

Most common adverse reactions in Study 10 and ARIEL2 (≥ 20%; Grade 1-4) were nausea (77%), asthenia/fatigue (77%), vomiting (46%), anemia (44%), constipation (40%), dysgeusia (39%), decreased appetite (39%), diarrhea (34%), abdominal pain (32%), dyspnea (21%), and thrombocytopenia (21%).

Most common laboratory abnormalities in Study 10 and ARIEL2 (≥ 35%; Grade 1-4) were increase in creatinine (92%), increase in alanine aminotransferase (ALT) (74%), increase in aspartate aminotransferase (AST) (73%), decrease in hemoglobin (67%), decrease in lymphocytes (45%), increase in cholesterol (40%), decrease in platelets (39%), and decrease in absolute neutrophil count (35%).

Co-administration of rucaparib can increase the systemic exposure of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, which may increase the risk of toxicities of these drugs. Adjust dosage of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, if clinically indicated. If co-administration with warfarin (a CYP2C9 substrate) cannot be avoided, consider increasing frequency of international normalized ratios (INR) monitoring.

Because of the potential for serious adverse reactions in breast-fed children from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the last dose.

You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. You may also report side effects to Clovis Oncology, Inc. at 1-844-258-7662.

Please see Brief Summary of Prescribing Information on the following pages.

Rubraca® (rucaparib) 300 mg tablets

RUBRACA® (rucaparib) tablets, for oral use

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE

Maintenance Treatment of Recurrent Ovarian Cancer

Rubraca is indicated for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

Treatment of BRCA-mutated Ovarian Cancer After 2 or More Chemotherapies

Rubraca is indicated for the treatment of adult patients with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for Rubraca *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic Syndrome (MDS)/Acute Myeloid Leukemia (AML) occur uncommonly in patients treated with Rubraca, and are potentially fatal adverse reactions. In approximately 1100 treated patients, MDS/AML occurred in 12 patients (1.1%), including those in long term follow-up. Of these, 5 occurred during treatment or during the 28 day safety follow-up (0.5%). The duration of Rubraca treatment prior to the diagnosis of MDS/AML ranged from 1 month to approximately 28 months. The cases were typical of secondary MDS/cancer therapy-related AML; in all cases, patients had received previous platinum-containing chemotherapy regimens and/or other DNA damaging agents.

Do not start Rubraca until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood counts for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities (> 4 weeks), interrupt Rubraca or reduce dose according to Table 1 *[see Dosage and Administration (2.2) in the full Prescribing Information]* and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks or if MDS/AML is suspected, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Rubraca.

Embryo-Fetal Toxicity

Rubraca can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings from animal studies. In an animal reproduction study, administration of rucaparib to pregnant rats during the period of organogenesis resulted in embryo-fetal death at exposures that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended human dose of 600 mg twice daily. Apprise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1) in the full Prescribing Information]*.

ADVERSE REACTIONS

The following serious adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Maintenance Treatment of Recurrent Ovarian Cancer

The safety of Rubraca for the maintenance treatment of patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer was investigated in ARIEL3, a randomized (2:1), double-blind, placebo-controlled study in which 561 patients received either Rubraca 600 mg BID (n=372) or placebo (n=189) until disease progression or unacceptable toxicity. The median duration of study treatment was 8.3 months (range: < 1 month to 35 months) for patients who received Rubraca and 5.5 months for patients who received placebo.

Dose interruptions due to an adverse reaction of any grade occurred in 65% of patients receiving Rubraca and 10% of those receiving placebo; dose reductions due to an adverse reaction occurred in 55% of Rubraca patients and 4% of placebo patients. The most frequent adverse reactions leading to dose interruption or dose reduction of Rubraca were thrombocytopenia (18%), anemia (17%), nausea (15%), and fatigue/asthenia (13%).

Discontinuation due to adverse reactions occurred in 15% of Rubraca patients and 2% of placebo patients. Specific adverse reactions that most frequently led to discontinuation in patients treated with Rubraca were anemia (3%), thrombocytopenia (3%) and nausea (3%).

Table 1. Adverse Reactions in ARIEL3 Occurring in ≥ 20% of Patients

Adverse reactions	Rubraca N=372		Placebo N=189	
	Grades[a] 1-4 %	Grades 3-4 %	Grades[a] 1-4 %	Grades 3-4 %
Gastrointestinal Disorders				
Nausea	76	4	36	0.5
Abdominal pain/distention[b]	46	3	39	0.5
Constipation	37	2	24	1
Vomiting	37	4	15	1
Diarrhea	32	0.5	22	1
Stomatitis[b]	28	1	14	0.5
General Disorders and Administration Site Conditions				
Fatigue/asthenia	73	7	46	3
Skin and Subcutaneous Tissue Disorders				
Rash[b]	43	1	23	0
Nervous System Disorders				
Dysgeusia	40	0	7	0
Investigations				
AST/ALT elevation	38	11	4	0
Blood and Lymphatic System Disorders				
Anemia	39	21	5	0.5
Thrombocytopenia	29	5	3	0
Neutropenia	20	8	5	1
Respiratory, Thoracic, and Mediastinal Disorders				
Nasopharyngitis/Upper respiratory tract infection[b]	29	0.3	18	1
Metabolism and Nutrition Disorders				
Decreased appetite	23	1	14	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

[b] Consists of grouped related terms that reflect the medical concept of the adverse reaction.

Adverse reactions occurring in < 20% of patients treated with Rubraca include headache (18%), dizziness (19%), dyspepsia (19%), insomnia (15%), dyspnea (17%), pyrexia (13%), peripheral edema (11%), and depression (11%).

Table 2. Laboratory Abnormalities in ARIEL3 Occurring in ≥ 25% of Patients

Laboratory Parameter[a]	Rubraca N=372		Placebo N=189	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Chemistry				
Increase in creatinine	98	0.3	90	0
Increase in cholesterol	84	4	78	0
Increase in ALT	73	7	4	0
Increase in AST	61	1	4	0
Increase in Alkaline Phosphatase	37	0.3	10	0
Hematology				
Decrease in hemoglobin	88	13	56	1
Decrease in platelets	44	2	9	0
Decrease in leukocytes	44	3	29	0
Decrease in neutrophils	38	6	22	3
Decrease in lymphocytes	29	5	20	3

[a] Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.

Treatment of BRCA-mutated Recurrent Ovarian Cancer After 2 or More Chemotherapies

Rubraca 600 mg twice daily as monotherapy has also been studied in 377 patients with epithelial ovarian, fallopian tube or primary peritoneal cancer who have progressed after 2 or more prior chemotherapies in two open-label, single arm trials. In these patients, the median age was 62 years (range: 31 to 86), 100% had an ECOG performance status of 0 or 1, 38% had *BRCA*-mutated ovarian cancer, 45% had received 3 or more prior lines of chemotherapy, and the median time since ovarian cancer diagnosis was 43 months (range: 6 to 197).

Table 3. Adverse Reactions Reported in ≥ 20% of Patients with Ovarian Cancer After ≥ 2 Chemotherapies Treated with Rubraca in Study 10 and ARIEL2

Adverse Reaction	All Ovarian Cancer Patients (N = 377) %	
	Grades[a] 1-4	Grades 3-4
Gastrointestinal Disorders		
Nausea	77	5
Vomiting	46	4
Constipation	40	2
Diarrhea	34	2
Abdominal Pain	32	3
General Disorders		
Asthenia/Fatigue	77	11
Blood and Lymphatic System Disorders		
Anemia	44	25
Thrombocytopenia	21	5
Nervous System Disorders		
Dysgeusia	39	0.3
Metabolism and Nutrition Disorders		
Decreased appetite	39	3
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea	21	0.5

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03).

The following adverse reactions have been identified in < 20% of the 377 patients treated with Rubraca 600 mg twice daily: dizziness (17%), neutropenia (15%), rash (includes rash, rash erythematous, rash maculopapular and dermatitis) (13%), pyrexia (11%), photosensitivity reaction (10%), pruritus (includes pruritus and pruritus generalized) (9%), Palmar-plantar erythrodysaesthesia syndrome (2%), and febrile neutropenia (1%).

Table 4. Laboratory Abnormalities Reported in ≥ 35% of Patients with Ovarian Cancer After ≥ 2 Chemotherapies Treated with Rubraca in Study 10 and ARIEL2

Laboratory Parameter	All Patients with Ovarian Cancer (N = 377) %	
	Grade 1-4[a]	Grade 3-4
Clinical Chemistry		
Increase in creatinine	92	1
Increase in ALT[b]	74	13
Increase in AST[b]	73	5
Increase in cholesterol	40	2
Hematologic		
Decrease in hemoglobin	67	23
Decrease in lymphocytes	45	7
Decrease in platelets	39	6
Decrease in absolute neutrophil count	35	10

[a] At least one worsening shift in CTCAE grade and by maximum shift from baseline.
[b] Increase in ALT/AST led to treatment discontinuation in 0.3% of patients (1/377).

DRUG INTERACTIONS

Effect of Rucaparib on Cytochrome p450 (CYP) Substrates

Co-administration of rucaparib can increase the systemic exposure of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*, which may increase the risk of toxicities of these drugs.

Adjust dosage of CYP1A2, CYP3A, CYP2C9, or CYP2C19 substrates, if clinically indicated. If co-administration with warfarin (a CYP2C9 substrate) cannot be avoided, consider increasing the frequency of international normalized ratio (INR) monitoring.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, Rubraca can cause fetal harm when administered to pregnant women. There are no available data in pregnant women to inform the drug-associated risk. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposures that were 0.04 times the $AUC_{0\text{-}24h}$ in patients receiving the recommended dose of 600 mg twice daily *[see Data]*. Apprise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In a dose range-finding embryo-fetal development study, pregnant rats received oral doses of 50, 150, 500, or 1000 mg/kg/day of rucaparib during the period of organogenesis. Post-implantation loss (100% early resorptions) was observed in all animals at doses greater than or equal to 50 mg/kg/day (with maternal systemic exposures approximately 0.04 times the human exposure at the recommended dose based on $AUC_{0\text{-}24h}$).

Lactation

Risk Summary

There is no information regarding the presence of rucaparib in human milk, or on its effects on milk production or the breast-fed child. Because of the potential for serious adverse reactions in breast-fed children from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks following the last dose.

Females and Males of Reproductive Potential

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating Rubraca.

Contraception

Females

Rubraca can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Rubraca.

Pediatric Use

The safety and effectiveness of Rubraca in pediatric patients have not been established.

Geriatric Use

In clinical studies 40% (297/749) of patients with ovarian cancer treated with Rubraca were 65 years of age or older and 9% (65/749) were 75 years or older. Grade 3-4 adverse reactions occurred in 65% of patients 65 years or older and in 63% of patients 75 years or older. For patients 65 years or older, the most common Grade 3-4 adverse reactions were anemia, fatigue/asthenia, and ALT/AST increase. No major differences in safety were observed between these patients and younger patients for the maintenance treatment of recurrent ovarian cancer or for the treatment of BRCA-mutated ovarian cancer after two or more chemotherapies.

Hepatic Impairment

No starting dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin less than or equal to upper limit of normal [ULN] and AST greater than ULN, or total bilirubin between 1.0 to 1.5 times ULN and any AST). No recommendation for starting dose adjustment is available for patients with moderate to severe hepatic impairment (total bilirubin greater than 1.5 times ULN) due to a lack of data *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Renal Impairment

No starting dose adjustment is recommended for patients with mild to moderate renal impairment (baseline creatinine clearance [CLcr] between 30 and 89 mL/min, as estimated by the Cockcroft-Gault method). There is no recommended starting dose for patients with CLcr less than 30 mL/min or patients on dialysis due to a lack of data *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

OVERDOSAGE

There is no specific treatment in the event of Rubraca overdose, and symptoms of overdose are not established. In the event of suspected overdose, physicians should follow general supportive measures and should treat symptomatically.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

MDS/AML: Advise patients to contact their healthcare provider if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. These may be signs of hematological toxicity or a more serious uncommon bone marrow problem called 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukemia' (AML) which have been reported in patients treated with Rubraca *[see Warnings and Precautions (5.1) in the full Prescribing Information]*.

Embryo-Fetal Toxicity: Advise females to inform their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1) in the full Prescribing Information]*. Advise females of reproductive potential to use effective contraception during treatment and for 6 months after receiving the last dose of Rubraca *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

Photosensitivity: Advise patients to use appropriate sun protection due to the increased susceptibility to sunburn while taking Rubraca *[see Adverse Drug Reactions (6.1) in the full Prescribing Information]*.

Lactation: Advise females not to breastfeed during treatment and for 2 weeks after the last dose of Rubraca *[see Use in Specific Populations (8.2) in the full Prescribing Information]*.

Dosing Instructions: Instruct patients to take Rubraca orally twice daily with or without food. Doses should be taken approximately 12 hours apart. Advise patients that if a dose of Rubraca is missed or if the patient vomits after taking a dose of Rubraca, patients should not take an extra dose, but take the next dose at the regular time *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

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REIMBURSEMENT

Forward-Thinking Insurers Adopt Genomics; Medicare Takes Perilous, Costly Leap Backward

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Blue Shield of California, Anthem, and Aetna now cover verification testing for pathogenic *BRCA*1 and *BRCA*2 findings reported out by 23andMe[4], and it is expected that more insurers will jump on this trend. Why? Because this is a wise business decision and allows insurers to take advantage of genomic data their insured already have in their hands.

These forward-thinking insurers are helping consumers use these data by creating a pathway to integrate their genomics into their care. True, these DTC data are not thorough or medical grade and should not be used to guide medical management, nor should they be used as a first-line test for any patient with a personal and/or family history of a condition that may be hereditary. But if the consumer stumbles across a condition that may affect care, such as hereditary cancer, hemochromatosis, or cardiac disease, it behooves both the consumer and the insurer to verify that finding's accuracy. Consumer-driven testing is uncovering powerful pieces of data that should not be pushed to the wayside or incorporated into medical care without verification.

CMS has chosen to use the narrowest of definitions when evaluating whether a patient has "signs and/or symptoms" of a condition and will not consider family history even when a hereditary cancer syndrome has already been identified in a family.

Instead, these data must be verified in a medical-grade lab. Before selecting the most appropriate validation test, a detailed personal and family history should be explored to determine whether other genetic tests may be appropriate for the consumer and his or her family. As more DTC companies begin to return health information to their consumers, consumer-facing workflows that support third-party, accurate genetic counseling and testing processes for verification will be necessary.[5] Insurers and corporate wellness programs (eg, Welltok, Sprout, Sharecare) will likely be involved in offering these services.

Amid all of this forward progress, CMS has chosen to maintain a costly and poorly timed stance from the dark ages. CMS is already known for not recognizing certified genetic counselors (CGCs) as healthcare providers. This is an expensive mistake for US patients and taxpayers because it is well known that CGCs are expert at assessing which patients need genetic testing and determining which tests would be most effective and least expensive.[6] CMS should instead embrace recognizing CGCs as healthcare providers and use CGCs as genetic usage specialists whenever possible.

For decades, CMS has been known for its outdated, poorly written criteria for genetic testing. As an example, CMS refuses coverage for cancer genetic testing for any of its insured until that person develops cancer, depriving that patient of the opportunity to avoid developing cancer or detect it earlier by knowing his or her hereditary cancer genetic status and choosing high-risk surveillance or prophylactic surgery[7] (**Table 1**).

CMS has chosen to use the narrowest of definitions when evaluating whether a patient has "signs and/or symptoms" of a condition and will not consider family history even when a hereditary cancer syndrome has already been identified in a family.[8] This costly decision means that a CMS patient who is clearly at risk for a hereditary cancer syndrome may not pursue a genetic test that costs several hundred dollars because it would be a costly out-of-pocket expense and, instead, may develop a cancer that costs the Medicare system hundreds of thousands of dollars in diagnostic testing, surgery, radiation, chemotherapy, hospitalizations, and long-term care. This does not include needless pain and suffering of the patient and the family, missed wages and childcare expenses for the patient and family, and, potentially, death. Men have been unfairly discriminated against under CMS criteria, most often deprived of *BRCA* testing unless they have already developed breast cancer, pancreatic cancer with Jewish ancestry, or prostate cancer (Gleason score ≥7)/pancreatic cancer with significant family history. These criteria are more restrictive than those proposed by the National Comprehensive Cancer Network (NCCN), which issues guidelines developed by panels of oncology and genetics experts.[9]

To rub salt in the wound, many stakeholders were concerned that CMS proposed to make their inadequate criteria even worse last year by refusing next-generation sequencing (NGS)–based genetic testing for cancer patients unless they had stage III or IV disease.[10] This decision making would be flawed because it would deprive people with early-stage disease, who would likely survive their cancers, of the chance to learn whether their cancer is hereditary and the opportunity for early detection or prevention of additional cancers associated with that hereditary syndrome. In response to the understandable backlash, the CMS reopened this national coverage determination (NCD) for comment from April 29 to May 29, clarifying that the proposed change was intended to apply in a germline setting only when testing is ordered for the purpose of guiding targeted cancer treatment. Some of this confusion may stem from the fact that guidance regarding germline testing is being derived from an NCD that was initially meant to apply to somatic testing only. A drafted decision is expected at the end of October 2019.[11]

There was also concern that this decision would negatively affect laboratories because CMS made its November 2018 ruling retroactive to March 2018. Over those 9 months, labs advised on coverage based on existing guidelines, performed NGS tests, and billed Medicare in accordance with existing guidelines and contracts. By implementing a retroactive decision, labs could be forced to pay back Medicare any fees for service collected during that period. Failing to do so could result in large financial penalties and damage the financial stability of labs preforming hereditary cancer testing. Thankfully, CMS has delayed "implementation" of these rules. It would be wise for them to delay them indefinitely.

Table 1. Indications for *BRCA1* and *BRCA2* Testing Covered by Medicare

CRITERIA FOR TESTING

- Individual with breast, ovarian[a], pancreatic, or prostate cancer from a family with a known deleterious *BRCA*1 or *BRCA*2 gene mutation
- Individual with a personal history of ovarian[a] cancer
- Individual with a breast cancer diagnosis meeting any of the following criteria:
  - Diagnosed ≤45 years[b]
  - Triple negative breast cancer (estrogen receptor negative, progesterone receptor negative, and human epidermal growth factor receptor 2 negative breast cancer diagnosed ≤60 years
  - Diagnosed at ≤50 years with:
    - An additional breast cancer primary
    - ≥1 first-, second-, or third-degree relative[c] with breast cancer at any age or
    - ≥1 first-, second-, or third-degree relative[c] with prostate cancer (Gleason score ≥7) or
    - An unknown or limited family history[d]
  - Breast cancer diagnosed at any age and
    - ≥1 first-, second-, or third-degree relative[c] with breast cancer ≤50 years or
    - ≥1 first-, second-, or third-degree relative[c] with ovarian cancer at any age or
    - ≥1 first-, second-, or third-degree relative[c] with metastatic prostate cancer or pancreatic cancer at any age
    - ≥2 additional diagnoses of breast cancer at any age in patient and/or in close blood relative[c] or
    - A first-, second-, or third-degree male relative with breast cancer
    - For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish[e]), no additional family history may be required.
  - Male breast cancer
- Personal history of prostate cancer (Gleason score≥7) at any age with:
  - ≥1 first-, second-, or third-degree relative[c] with ovarian cancer at any age or
  - ≥1 first-, second-, or third-degree relative[c] with breast cancer ≤50 years or
  - ≥1 first-, second-, or third-degree relative[c] with pancreatic cancer at any age or
  - ≥1 first-, second-, or third-degree relative[c] with metastatic prostate cancer at any age or
  - ≥2 first-, second-, or third-degree relatives[c] with breast cancer and/or pancreatic cancer and/or prostate cancer (Gleason score ≥7 or metastatic) at any age or
  - Ashkenazi Jewish ancestry
- Personal history of pancreatic cancer at any age
- Personal history of metastatic prostate cancer (radiographic evidence of or biopsy-proven disease)
- *BRCA1/2* pathogenic mutation detected by tumor profiling on any tumor type in the absence of germline mutation analysis

NOTES

a. Includes fallopian tube and primary peritoneal cancers. *BRCA*–related ovarian cancers are associated with epithelial, nonmucinous histology.
b. Two breast cancer primaries includes bilateral (contralateral) disease or 2 or more clearly separate ipsilateral primary tumors either synchronously or asynchronously.
c. The National Comprehensive Cancer Network defines blood relative as first- (parents, siblings, and children), second- (grandparents, aunts, uncles, nieces, and nephews, grandchildren, and half-siblings), and third-degree (great-grandparents, great-aunts, great-uncles, great-grandchildren and first cousins) relatives on same side of family.
d. Medicare will cover *BRCA*-testing for an adopted individual patient's medical record, and documentation of genetic counseling prior to *BRCA* testing.
e. Testing for Ashkenazi Jewish founder-specific mutations should be performed first. Comprehensive *BRCA1/2* testing may be considered if ancestry also includes non-Ashkenazi Jewish relatives or if any of the other *BRCA*-related criteria are met.

Numerous other contradictions and loopholes have been found throughout the NCD documentation.[12] For example, the NCD blocks NGS-based testing for women with early-stage disease, yet it does not block Sanger or polymerase chain reaction (PCR)–based testing in these patients. Similarly, NGS testing of multiple genes (within a certain category) is directed to be billed under an umbrella code instead of stacked individually. However, this umbrella code doesn't apply to Sanger or PCR-based testing, creating a loophole for laboratories and the potential to bill for up to 9 genes individually ("stacked"), which is much less cost-efficient. Experts have found multiple other such inconsistencies within the NCD.[13]

What can be done to fix the CMS crisis? First, CMS should hire a CGC with experience in the payer system to serve as a director in genetics. This individual should oversee review and revamping of all testing criteria. Most expert guidelines, including those from NCCN and the US Preventive Services Task Force, stress the importance of family history as part of a comprehensive genetics evaluation, and no expert guidelines consider cancer stage to be an indicator of possible hereditary contribution to disease.[14,15] CMS should also immediately recognize CGCs as healthcare providers. Of note, the Access to Genetic Counselors Services Act of 2019, recently introduced in the Congress, would require that genetic counselors be reimbursed by Medicare for providing counseling services.[16]

Genetic counselors and providers must also recognize their role in this process: namely, this is just CMS guidance. We often assume that if CMS denies a claim, secondary insurance will too. However, the secondary insurance does not have to deny it unless the claim is specifically excluded. This means that we should and must appeal. This can be time-consuming and annoying, but it may make a difference, and claims may be approved on the second or third appeal. Why is this important? Because it affects a plan's overall star rating. If a plan has many denials successfully overturned, its rating may be lowered, making it harder for the insurer to market itself and recruit new members. CMS plans care about this rating. Appeal your patients' claims at every level, and allocate resources within your department to streamline this process with template letters. Laboratories that have dedicated reimbursement departments can and must be an active part of this solution, ensuring that appropriate and legal coding/billing practices are used in the claims appeal process. Collect cases that were not covered and should have been, and publish them as Yang et al did last year (**Table 2**).[17-20] Spread the word about these cases—without protected health information, of course—on social media and tag the insurer.

Genetic counselors and providers can also be part of the solution by being proactive, positive, and collaborative. Genetics is moving too quickly for payers to be up-to-date on best practices. These payers are not in the field seeing patients and often do not see or understand the gaps that their policies create. They are not genetics experts and need relationships with professional societies, such as the National Society of Genetic Counselors, the American Society of Human Genetics, and the American College of Medical Genetics to provide fast and efficient guidance. These societies would be wise to create small internal committees of genetics providers with expertise in payer relations and then reach out to each payer—including CMS—to offer their services in reviewing policies and providing guidance around them. We should offer to speak at payer meetings and develop relationships with decision makers within these plans. To take advantage of the promise of genomics and precision medicine, insurers and genetics experts must be willing to work together to create policies that are effective, efficient, and fair to all parties involved. ◆

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Table 2. Efficacy of Medicare *BRCA* Testing Guidelines for Identification of Pathogenic/Likely Pathogenic Variant Carriers in Context of Historical Observations of At-Risk Versus Identified *BRCA* Carriers[17]

Cohort	Proportion/ Rate
Percentage of *BRCA* carriers that have been identified and informed[18]	10%
Percentage of individuals at risk to have *BRCA*-related cancer syndrome who have not been tested[19,20]	50%-80%
Rates of pathogenic/likely pathogenic variants in patients who met Medicare *BRCA* testing criteria vs those who did NOT meet criteria and were found to have a pathogenic/likely pathogenic variant in a NCCN-designated breast and/or ovarian cancer gene[17]	8.4% vs 6.2%

educator, lecturer, media spokesperson, and advocate, notably as a plaintiff in the 2013 *BRCA* gene patent case decided by the Supreme Court of the United States in 2013, *Association for Molecular Pathology et al v Myriad Genetics.* The decision led to dramatically reduced prices for genetic testing and allowed more patients to gain access to this technology. Matloff founded My Gene Counsel and its digital tools to be used alongside genetic testing to ensure that results are used accurately and effectively.

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ADVOCACY

The Impact of Germline Testing for Hereditary Cancer Postdiagnosis

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The most common mutations are among Lynch syndrome and *BRCA1/2* genes, affecting approximately 1 in 279 and 1 in 400 Americans, respectively.[1,2] For women with germline mutations in *BRCA1* or *BRCA2*, the risk of breast cancer by age 80 is 72% for *BRCA1* carriers and 69% for *BRCA2* carriers,[3] compared with 13% for the general population. [4] Similarly, the risk of ovarian cancer rises from a lifetime risk of 1.3% in the general population[3] to a risk of 44% for *BRCA1* carriers and 17% for *BRCA2* carriers.[4] For those with mutations in Lynch syndrome genes, lifetime risk of colorectal cancer is up to 68%[5] versus 4.2% in the general population.[3] Lynch syndrome is also associated with elevated risk of endometrial cancer (up to 60% lifetime risk versus 2.7% in the general population) and ovarian cancer (up to 24% lifetime risk) depending on which Lynch gene is mutated.[6] Among those with pancreatic cancer, 5.5% have inherited mutations in a high-risk cancer gene.[7] Up to 10% of men with advanced prostate cancer have a pathogenic mutation in a cancer-predisposing gene.[8]

NATIONAL GUIDELINES FOR GENETIC TESTING

Evidence-based guidelines and recommendations from a broad range of professional societies support the use of germline genetic testing in certain patients. The National Comprehensive Cancer Network (NCCN) provides guidelines that outline how to best screen for, prevent, and treat cancer, including determining who should be offered genetic testing for hereditary cancer risk and how individuals should be followed after testing. The American Society of Clinical Oncology states that recognition and management of individuals with an inherited susceptibility to cancer are core elements of oncology care.[9] The Society of Gynecologic Oncology (SGO) recommends genetic testing for all women who received diagnoses of epithelial ovarian, tubal, and peritoneal cancers, even in the absence of a family history.[10] Additionally, SGO guidelines indicate that all women who receive a diagnosis of endometrial cancer should undergo systematic clinical screening for Lynch syndrome and/or molecular screening when resources are available.[11] The American Society of Breast Surgeons recommends genetic testing for all patients with a personal history of breast cancer. This group also suggests updated testing for previously tested patients for whom no pathogenic variant was identified.[12] The American College of Medical Genetics and National Society of Genetic Counselors offer guidelines on referral and testing for 28 of the most common hereditary cancer susceptibility syndromes.[13]

CLINICAL UTILITY OF GERMLINE TESTING FOR INDIVIDUALS WITH CANCER DIAGNOSES

For many hereditary cancers, knowledge of a pathogenic mutation prior to the onset of cancer can inform screening, result in earlier detection of cancer at more treatable stages, and allow prevention options such as prophylactic surgery. For those with cancer, germline testing informs choices for care and treatment. Importantly, knowledge of an inherited mutation can alert extended family members to their cancer risk.

Among those with cancer diagnoses, heritable mutations confer significant risk of increased morbidity and additional primary cancers. This information gives physicians more accurate assessments of cancer risk for other organs and allows tailoring of healthcare strategies that may reduce the morbidity and mortality associated with these syndromes.

The following are a few examples where knowledge of a pathogenic mutation conveys clinically actionable interventions for those who have cancer.

PAN-TUMOR CONSIDERATIONS

People with inherited mutations may respond differently to certain types of treatment regardless of the cancer site involved.

- In the case of patients with *BRCA1* and *BRCA2* germline mutations, a class of targeted therapies known as poly (ADP-ribose) polymerase (PARP) inhibitors has shown benefit for treating multiple tumor types. PARP inhibitors are approved for treating breast and ovarian cancer in people with germline *BRCA* mutations; however, ongoing research suggests that these drugs also may offer benefits for patients with pancreatic and prostate cancers.
  - » People with Lynch syndrome are more likely to have cancers with a genetic feature called microsatellite instability–high (MSI-H). Pembrolizumab is an immunotherapy with FDA approval to treat any MSI-H advanced cancers.[14]

Breast Cancer

Response to treatment differs significantly based on mutation status. For instance, *BRCA1* mutation carriers with hormone-negative breast cancers show less sensitivity to taxane chemotherapy.[15] Germline *BRCA* mutations are positive selection criteria for use of platinum-based regimen and potentially PARP inhibitors.[16] An estimated 20% of patient with triple-negative breast cancer (TNBC) are *BRCA* mutation carriers, and 70% of breast cancers that develop in *BRCA1* mutation carriers are triple-negative. A germline *BRCA* mutation has been used to identify patients with TNBC who will best respond to carboplatin therapy. As such, the *BRCA*-mutated TNBC subgroup should receive platinum derivatives as part of their neoadjuvant (and/or adjuvant) treatment.

A germline mutation may also affect surgical decision making in breast cancer. Although someone without a germline mutation may opt for lumpectomy and radiation, a woman with a *BRCA* or *PALB2*- mutation, for instance, would be advised to undergo a double mastectomy. Rates of contralateral breast cancer after either breast-conserving therapy or unilateral mastectomy are increased in women with *BRCA1/2* mutations compared with patients who have sporadic breast cancer. Similarly, women with breast cancer who test positive for a *BRCA* mutation are at significantly increased risk of developing ovarian cancer. Knowledge of this risk enables the patient and her healthcare team to be more aware and vigilant regarding additional primary cancers.

Colorectal Cancer

There is considerable stage-independent variability in colorectal cancer outcomes that may reflect variation in microsatellite instability (MSI) status. Many colorectal cancer patients benefit from MSI testing before the cancer is advanced or metastatic.[6] Lynch syndrome patients account for 3% of colorectal cancer patients.[17] Risk of uterine and ovarian cancer, as well as gastric, urinary tract, and small bowel cancer, rises in Lynch syndrome patients. Knowledge of these risks leads to greater patient and provider awareness, which may result in earlier diagnosis of additional primary cancers.

Ovarian Cancer

More than 1 in 5 ovarian carcinomas are associated with germline mutations, and approximately 15% are attributable to a *BRCA* mutation. An additional 5% to 6% are the result of a germline mutation in *BRIP1, RAD51D, RAD51C, PALB2, BARD1,TP53*, or a Lynch syndrome gene (*MLH1, MSH2, MSH6, PMS2*).[18]

> Studies confirm that women with germline *BRCA* cancers often behave and respond to treatment differently than sporadic cancers.[19] Specifically, ovarian cancer patients with with germline *BRCA* cancers have a better response to platinum therapy compared with patients who do not have *BRCA* mutations.[20] Likewise, *BRCA* mutation carriers appear to be more sensitive to the benefits of intraperitoneal chemotherapy.[21,22]

Prostate Cancer

Germline testing may have significant diagnostic and therapeutic utility for patients with prostate cancer, as demonstrated by the identification of pathogenic germline alterations in men with castration-resistant prostate cancer who respond to PARP inhibition as suggested by clinical trials.[23] Aggressive therapy in early-stage *BRCA*-positive prostate cancers, particularly those with germline *BRCA2* mutations, is indicated. This includes a combination of early radical local treatment (eg, radical prostatectomy or radiotherapy) with adjuvant systemic therapy. A 2018 study confirmed that much like *BRCA2*-related breast and ovarian cancers, men with *BRCA2*-associated castration-resistant prostate cancers respond better to carboplatin-based chemotherapy than do men with non–BRCA-positive prostate cancers.

> There is growing evidence of the presence of germline mutations in men with prostate cancer and the clinical utility of these findings. A recent study reported in *JAMA Oncology* by Nicolosi et al found that 17% of men with prostate cancer had germline genetic mutations. *BRCA* variants accounted for more than 30% of the mutations, and a number of variants with known therapeutic implications (*CHEK2, ATM, PALB2, MUTYH*, etc.) were identified.[23] Testing men with earlier-stage disease who meet family history criteria offers an opportunity to provide the appropriate treatment regimen and inform them about their increased risk of other cancers.

In addition to guiding optimal surgical and therapeutic decisions, germline testing identifies patients for whom there may be contraindications. For instance, patients with Lynch syndrome with stage II MSI-H tumors do not benefit from fluorouracil adjuvant therapy.[24] In the case of breast cancer, patients who are not carriers of a *BRCA1/2* mutation are suitable for accelerated partial breast irradiation.[25]

HEALTH INSURANCE COVERAGE OF GENETIC TESTING

The Affordable Care Act requires insurance companies to pay for both genetic counseling and *BRCA* testing as a preventive service for women who meet certain criteria. For these patients, insurance companies must cover the entire cost of genetic counseling and *BRCA* testing with no out-of-pocket costs to the individual. This includes testing in women who have previously received a cancer diagnosis, provided they do not have active disease and are not in treatment.

MEDICARE COVERAGE OF GENETIC TESTING

Recently, there have been changes to the Medicare national coverage determinations (NCDs) 90.2 to more narrowly define coverage of next-generation sequencing (NGS) testing.[26,27,28] (See related story on **SP288**.)

Coverage has been interpreted to cover patients who meet these 3 criteria:

- They have recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer
- They have not been previously tested using the same NGS test for the same primary diagnosis of cancer or had repeat testing using the same NGS test but only when a new primary cancer diagnosis is made by the treating physician
- They have decided to seek further cancer treatment (eg, therapeutic chemotherapy)

These criteria are overly restrictive, because germline testing has significant value beyond identifying those who may benefit from current FDA-approved targeted treatments.

Prior to implementation of this policy, local coverage determinations (LCDs) provided for germline genetic testing of Medicare beneficiaries who met established, evidence-based criteria. The LCDs were designed to provide reasonable and necessary medical care. The NCD overrides these policies and significantly limits testing for germline mutations. Cancer is recognized as a disease of older adults, with more than 50% of new cases being diagnosed after age 65. Although hereditary cancers often occur at younger ages, older-onset cancers also can have a familial component.[29,30] Germline testing should not be reserved only for those who have advanced or metastatic disease. The promise of personalized and precision medicine is the ability to detect cancer early—or prevent it altogether. This NCD fails to provide the standard of care to patients with cancer by limiting germline testing to those with recurrent, relapsed, refractory, metastatic, or advanced stage III or IV disease. An estimated 60% of cancers in the Medicare population are diagnosed at stage I or II. Although prevention is not Medicare's mandate, stopping early stage disease from advancing is a valuable and viable end point.

A 2018 study published in the *Annals of Surgical Oncology* found that "a substantial number of Medicare patients with clinically actionable genetic variants are being missed by current testing criteria" and suggested the need for significant expansion and simplification of the testing criteria for hereditary breast and ovarian cancer.[31] Many cancers related to germline mutations are treatable with therapies that are not specific to the mutation or disease—but the genetic variant affects treatment response and outcomes. A number of studies have shown that rates of genetic testing for hereditary cancer are well below what they should be, given current clinical guidelines—especially among minority populations.[32-39]

NGS-based germline testing has demonstrated utility in earlier cancer settings. Testing individuals who meet evidence-based criteria before they experience recurrence or have advanced stage disease serves the patient population by identifying the best treatment options regardless of disease stage.

In addition to guiding optimal surgical and therapeutic decisions, germline testing identifies patients for whom there may be contraindications.

Restriction of patient access to potentially life-saving tests raises significant concerns for FORCE. Knowledge of a germline mutation can benefit the individual, their family, and society in general. We hope that CMS will seriously consider the implications of this NCD and take steps to ensure that it does not have negative repercussions for the patient community in regard to access to care and the potential benefits of precision medicine. ◆

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PROVIDER PERSPECTIVE

Genetic Oncology Testing Is Complex, but Coverage and Reimbursement Don't Have to Be

Health Plans Often Struggle to Establish Coverage Policies for Genetic Tests to Identify and Guide Treatment for Cancer

L. Patrick James, MD

JAMES

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CONTINUED FROM COVER

HOW GENOMIC TESTING CREATES VALUE

Diagnostic laboratory services in an oncology setting can pose unique challenges, and it is important that payers understand these issues when making coverage and reimbursement decisions. For example, whereas some genetic tests are well validated and guideline supported, others might identify mutations that are uncommon or for which limited therapeutic interventions exist. In other cases, tests may not be rigorously evaluated or may even provide unclear or conflicting information. Some genetic tests may pose ethical or social implications.

Innovation in oncology is moving at a breakneck pace. Genetic testing can affect diagnosis and treatment, so it is imperative that payers reevaluate how they make coverage and reimbursement decisions for services as new evidence of their value emerges.

A health plan may employ several criteria to assess the value of a genetic test service. Health plans can leverage one or more of the many frameworks designed to guide test assessment.

The CDC's Office of Public Health Genomics established and supported the ACCE Model Project, which developed the first publicly available analytical process for evaluating scientific data on emerging genetic tests. The ACCE model, which gets its name from the 4 main criteria (analytic validity, clinical validity, clinical utility, and ethical, legal and social implications), helps payers navigate the challenges of genetic testing to determine which tests provide true value.

The ACCE framework has been used in the United States and worldwide for evaluating genetic tests. It includes collecting, evaluating, interpreting, and reporting categorical evidence on particular genetic tests so that policy makers have access to current and reliable information. The ACCE process comprises a standard set of 44 targeted questions that frame each of the major categories. Questions also address the nature of the disorder, the clinical setting, and the type of testing. Ethical, legal, and social considerations are a component of the evaluation of clinical utility.

- **Analytic validity** refers to technical test performance—the ability to test accurately and reliably for the genetic variants of interest in the clinical laboratory in specimens that are representative of the population of interest. Analytic validity includes analytic sensitivity, analytic specificity, laboratory precision, and assay robustness.
- **Clinical validity** refers to the ability to identify or predict accurately and reliably the clinically defined disorder or phenotype of interest. Clinical validity encompasses clinical sensitivity and specificity and predictive values of positive and negative tests that take into account the prevalence of the disorder.
- **Clinical utility** refers to the evidence that the genetic test improves clinical outcomes and adds value for patient-management decision making compared with current management without genetic testing.
- **Ethical, legal, and social implications** addresses the fact that unique characteristics make genetic testing especially prone to ethical, legal, and social issues. For example, genetic information is permanent, and a patient must be prepared to assimilate new information, knowing that it cannot be taken back or changed. This can be a source of anxiety for those who do not contemplate the value of the information and its impact on their lives. Genetic information is also often predictive. There are psychological, financial, and social risks of learning one's personal or reproductive risk for a genetic disorder. Genetic test results may also affect relatives who may or may not want to know this information.

Several additional factors are considered, such as access to downstream remedies or actions, access for vulnerable populations, quality assurance measures, educational materials, and evaluation of program performance.[2]

Innovation in oncology is moving at breakneck pace. Genetic testing can affect diagnosis and treatment, so it is imperative that payers reevaluate how they make coverage and reimbursement decisions for services as new evidence of their value emerges.

NOT ALL LAB TESTING IS THE SAME: THE CASE FOR RESPONSIBLE LAB TESTING

Making coverage and reimbursement decisions for a genetic test should never occur outside the context of the laboratory provider that offers it.

Determining whether or how to reimburse is as complex as the testing itself. However, payers can take 4 simple steps to ensure they both provide patients access to the care they need and are responsible to their business.

1. **Partner with lab service providers with clinical genetics expertise.** Physicians struggle to identify appropriate test services and interpret results. Next-generation sequencing

(NGS), an advanced technique of identifying gene variants, is a mainstay of today's cancer testing for solid tumors and hereditary cancers. However, according to the results of 1 survey of oncologists, 11% of respondents found NGS test results very difficult to interpret, and 40% found NGS test results difficult to interpret sometimes.[3] At Quest Diagnostics, a team of medical directors and genetic counselors is on hand to help physicians navigate the complexities of genetic testing, guiding test selection and results interpretation.

2. **Select panels based on quality, not quantity.** Some lab providers offer test panels with several hundreds of genes. Yet, for most cancers, the number of actionable genes, based on current evidence, is just a few dozen. Providing coverage and reimbursement for test services based on actionable genes will reduce waste—and lower the risk of improper care. Quest focuses on developing panels that provide actionable insight to influence precision care panels based on the ACCE framework.

3. **Use tests designed for clinical practice.** For patients today, purchasing a genetic test to assess cancer risk is as easy as clicking to place it in an Amazon shopping cart. However, consumer genetic tests may not always meet the same level of rigor as clinical services. A recent study found that an FDA-cleared consumer genetic test that identifies 3 founder mutations of the *BRCA1/2* genes would miss nearly 90% of patients with mutations associated with hereditary breast and ovarian cancers.[4]

4. **Chose providers with bioinformatics expertise.** Lab testing today is a high-tech endeavor, with bioinformatics and data analytics driving the ability to sort through countless data to surface actionable information. Seek lab partners with a demonstrated commitment to turning information into insights—and a quality of information technology staff and infrastructure to support it. A test that isn't designed for clinical practice may miss a variable amount of content depending on genes, miss mutations, and have poor sensitivity or specificity.

Finally, when grappling with coverage and reimbursement decisions, it's most important to put the patient first. At the end of the day, healthcare is about patient care. This should be the guiding light that influences access to genetic testing. A patient who receives the right test at the right time may experience quicker access to therapy, better outcomes, and, ultimately, lower costs. Delaying access to a test or not providing access to a test that is optimal for a patient (eg, when a patient needs NGS instead of exome sequencing), can negatively affect patient health and increase costs. ◆

AUTHOR INFORMATION

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Coverage by Jaime Rosenberg

How Are States Dealing With Challenges Facing Patients With Cancer?

HIGH COSTS OF CARE, particularly for prescription drugs, dominated a discussion of cancer care at the state level during the June 27, 2019, National Comprehensive Cancer Network Policy Summit in Washington, DC.

With authority from CMS, states have looked at different ways to address needs for their specific populations while containing costs, explained Jennifer Carlson, associate vice president of External Relations and Advocacy at The Ohio State University Wexner Medical Center.

For example, states like Louisiana and Washington have adopted the "Netflix" subscription model, which allows the states to negotiate prices with manufacturers of hepatitis C virus (HCV) drugs. Under the model, states can pay a fixed amount per year for an unrestricted amount of HCV drugs.[1] States are also dabbling with value-based purchasing models, where the states pay different amounts based on the efficacy of the drug, Carlson explained.

While most of the focus has been on high drug costs, it's important to keep in mind that these are not the only costs affecting patients with cancer, said Lee Jones, MBA, a patient advocate and cancer survivor from Arlington, Virginia. Patients are also affected by the cost of radiation, computed tomography scans, and ongoing testing.

Offering a unique perspective, Anne Levine, MEd, MBA, vice president of external affairs, Dana-Farber Cancer Institute, discussed how Massachusetts controls healthcare spending by tying that spending to the state's economy. In 2006, the state passed legislation that led to 97% of the commonwealth's residents having insurance coverage by 2008.[2] Of those covered, 25% are enrolled in the state's Medicaid program, which accounts for 40% of the entire state budget, explained Levine.

With rapid growth in healthcare spending, the state in 2012 passed another piece of legislation to put healthcare spending in line with the growth of the state's overall economy by setting a healthcare cost growth benchmark set by the state's Health Policy Commission (HPC).[3] Total healthcare costs account for growth in all medical expenses paid to providers by private and public payers, all patient cost-sharing amounts, and the net cost of private insurance. Between 2013 and 2017, the benchmark was set equal to the potential gross state product of 3.6%.

Beginning in 2018 and ending in 2022, the benchmark is set to 3.1%. While overall healthcare spending must also be monitored, Massachusetts has found that pharmaceuticals account for a large part of healthcare spending growth, explained Levine. Between 2016 and 2017, overall healthcare costs grew 1.7%, but pharmacy expenditures increased by 4.1%.[4]

To try and rein in drug prices, the state is moving toward allowing MassHealth, the commonwealth's Medicaid program, to allow the program to negotiate directly with drug companies for high-priced drugs. When the plan was initially introduced in January, if the negotiations were not successful, the governor's office could propose a price, hold public hearings, or refer the drug price to the HPC.[5] In the final version, drug manufacturers would not be forced to negotiate prices, attend public hearings, or be referred to the Massachusetts' attorney general.

While innovative, the model could negatively impact patients with cancer, warned Jones.

"If you start capping expenditures on healthcare, it eventually ends up getting down to the patient, and the patient is not able to have access to the quality or quantity of care that they need," said Jones. "And if you end up capping it significantly enough, you may end up getting drug makers not being willing to sell drugs to that state if they can't earn whatever they consider to be a reasonable profit."

Moving the conversation outside of costs, the panel also discussed their frustrations with utilization management strategies, including prior authorization and step therapy.

"I think the intentions behind it are good in that we're trying to promote value and decrease waste, but I think the concerns most practitioners have is that limits our ability to individualize care and also, most importantly, causes delays in our patients' care," said Shiven B. Patel, MD, MBA, FACP, assistant professor in the Division of Oncology in the Department of Medicine at the Huntsman Cancer Institute at the University of Utah.

In the most extreme cases, said Patel, patients die waiting to get certain drugs approved. He gave the example of patients he's seen with lung cancer who have metastasis in the brain and need oral chemotherapy but have died waiting sometimes 4 to 6 weeks to get them approved.

The Huntsman Cancer Institute has hired a pharmacist whose sole job is to deal with the prior authorization process and patient assistance programs, "so our institutional costs are going up because we're hiring people just to help our patients access these meds," said Patel.

With stories like this and others, states around the country have taken the initiative to regulate these utilization management strategies. John Cox, DO, MBA, FACP, FASCO, medical director of Oncology Services at Parkland Health and Hospital System, University of Texas Southwestern, explained that the legislature recently passed several bills dealing with step therapy, one of which prohibits step therapy in metastatic breast cancer.[6]

Levine said Massachusetts currently has a bill pending that would implement a series of guardrails for step therapy, including allowing an exemption if it's part of an approved clinical guideline, allowing physicians to override the step therapy in certain instances, and implementing tight time frames for utilization management decisions to be made. ◆

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Shifting Regulatory Action to States: Implications for Patient Access to High-Quality Cancer Care

SINCE PRESIDENT DONALD TRUMP took office, his administration has been granting states greater flexibility in how they address healthcare for their populations. This involves Medicaid work requirements, block grants, and short-term, limited duration (STLD) health plans.

On June 27, a panel of diverse stakeholders gathered at the National Comprehensive Cancer Network Policy Summit in Washington, DC, to discuss how shifting regulatory signals from both the federal government and from states has implications for patient access to high-quality cancer care.

Panelists kicked off the discussion by outlining how states have leveraged Medicaid Section 1115 waivers to initiate different types of demonstration and research projects, such as Medicaid expansion and, more recently, Medicaid work requirements for certain populations.[1]

"I think it's a larger trend of states looking at really beginning to diversify the Medicaid population more and to say, 'We want to look at populations differently,'" said Nina Owcharenko Schaefer, senior research fellow at The Heritage Foundation. "Rather than having Medicaid as one program where we deliver [healthcare] to everyone, I think what we're seeing is states taking a very active role in understanding the needs of the patients in Medicaid are very different from one another, and that not every…Medicaid patient is the same as another Medicaid patient."

A number of states have looked at different ways to diversify their programs, such as by examining cost sharing for some of the higher income levels in Medicaid, addressing behavioral health, and looking beyond the medical scope to alternative services.

"From the patient perspective, flexibility is important and innovation is important; however, the concern—and we try to make sure there's a clear balance—is the fact that you have to have flexibility but also make sure that patient access and access to quality care is not harmed," said Keysha Brooks-Coley, MA, vice president of federal advocacy and strategic alliances at the American Cancer Society Cancer Action Network. She noted that Medicaid work requirements, in particular, could hinder access for patients with cancer.

The panel also discussed block grants, which have not yet seen as much uptake as work requirements. In March, Trump released his budget for fiscal year 2020, which called for converting Medicaid to a system of block grants.[2] On July 1, a law went into effect in Tennessee that directed the governor to submit a waiver to CMS to turn the state's Medicaid program into a block grant. If approved, Tennessee would become the first state to make the transition.[3]

Block grants represent the concept that states should figure out what best serves the needs of their populations, said Ronald S. Walters, MD, MBA, MHA, a professor of clinical medicine in the Department of Breast Medical Oncology, Division of Cancer Medicine, at The University of Texas MD Anderson Cancer Center, Houston. The idea makes sense as long as guardrails are built to make sure essential health benefits are protected, he added.

"States balance their budgets, so they are squeezed in figuring out how to take that dollar and make it spread everywhere," Schaefer said. "You know where they don't balance their budget? Here in Washington."

Consequently, she said, states shift additional costs to the federal government. Block grants are one way to put the federal government on a more reliable and consistent budget cycle. Some states also favor block grants because they like the idea of having the freedom to use funding how they see fit, even if it means a different style of funding, she said.

Brooks-Coley pushed back, arguing that there are a lot of concerns from the patient perspective. She posed the question: What happens when states run out of money or don't have enough to provide certain care for their populations?

The panel also discussed Section 1332 waivers, which eliminate certain requirements of the Affordable Care Act (ACA) and allow states to pursue alternative coverage approaches in the exchanges and small group markets that are consistent with the goals of the ACA.

The Trump administration has fostered a broader interpretation of these waivers, providing states more leeway in developing initiatives. According to Schaefer, multiple states have now used 1332 waivers to do risk adjustment, such as by using funding that goes to the subsidies within the exchanges and redirecting it to insurance plans that have high-risk and high-cost populations.

How and how often these waivers are used going forward will likely depend on the result of ongoing litigation involving the ACA, Walters said. In December 2018, a federal judge in Texas ruled that the ACA's individual mandate is unconstitutional and the rest of the law must also fall. In March, the Department of Justice backed the ruling.[4]

Even if the entire legislation is struck down, innovation waivers like 1332 waivers will continue, Walters argued. "They may not have the strength of the ACA, but this is an ongoing effort to give states much more authority and leeway to design what's important for that particular state," he said.

Bob Donnelly, MPP, senior director of health policy at Johnson & Johnson, also noted that ongoing efforts to erode the ACA are important in a system that now offers broader access to STLD health plans outside of what the ACA envisioned, which can create issues regarding benefits and the impact on risk pools.

In response, Schaefer argued that the plans offer opportunities for those getting "squeezed out of the current system," including many middle-class families that don't receive subsidies and are leaving the market as healthcare costs and premiums continue to rise. States have been on the frontline of this, seeing firsthand how their residents can't afford coverage, Schaefer said, adding that STLD plans provide immediate relief to these types of consumers. However, she predicted that, because of those plans' limitations, associated health plans and health reimbursement accounts will be more popular.

Although beneficial for some consumers, these plans are offered to everyone, said Brooks-Coley, arguing that consumers will often buy into them without fully understanding what they are and what they offer. Consumers buy plans they believe are cheaper and then get stuck with high out-of-pocket costs after getting sick with cancer, she said.

Rounding up the conversation, the panel touched briefly on value-based contracts, which have been touted as a way to address the high costs of cancer drugs, among others.

"There are still a lot of nuances to value-based contracting that people have to get experience in exactly how to do it. Intuitively, it seems very easy to do until you get into all the details, and it gets complicated very quickly," Walters said.

Donnelly agreed, adding that it is early in the playing field and that evaluating these contracts is just as important as actually enforcing them so that states can learn what works and what doesn't. ◆

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POLICY UPDATES

UK Cancer Group Warns That Obesity Is Overtaking Smoking as Disease Driver

ALTHOUGH SMOKING cigarettes is considered the most prevalent—yet preventable—cancer risk, new data suggest that people who are obese now outnumber people who smoke, and excess weight now causes more cases of certain cancers than smoking in the United Kingdom.

According to recent data, nearly one-third of UK adults are obese and overweight, which now holds a greater risk of developing 4 types of cancer compared with smoking.

"As smoking rates fall and obesity rates rise, we can clearly see the impact on a national health crisis when the government puts policies in place—and when it puts its head in the sand," Michelle Mitchell, Cancer Research UK's chief executive, said in a statement. "Scientists have so far identified that obesity causes 13 types of cancer, but the mechanisms aren't fully understood. So further research is needed to find out more about the ways extra body fat can lead to cancer."[1]

In the United Kingdom, data show that each year, excess weight causes around 1900 more cases of bowel cancer than smoking does. Similarly, there are 1400 more cases of kidney cancer, 460 more cases of ovarian cancer, and 180 more of liver cancer each year.[2]

Comparatively, in the United States, in 2011 to 2014, nearly 70% of adults were overweight or obese and more than one-third were obese, according to the National Cancer Institute.[3] In the United States, obesity is linked to increased risks of endometrial cancer, esophageal adenocarcinoma, gastric cardia cancer, liver cancer ,and others. Additionally, smoking has steadily declined in the United States since the mid-1960s, whereas obesity has been rising, according to America's Health Rankings.[4]

"There isn't a silver bullet to reduce obesity, but the huge fall in smoking over the years—partly thanks to advertising and environmental bans—shows that government-led change works. It was needed to tackle sky-high smoking rates and now the same is true for obesity," noted Linda Bauld, professor of public health at The University of Edinburgh in Scotland. "The world we live in doesn't make it easy to be healthy, and we need government action to fix that, but people can also make changes themselves—small things like swapping junk food for healthier options and keeping active can all add up to help reduce cancer risk."

Cancer Research UK launched a campaign to increase the awareness of the obesity-related cancer risk. The campaign suggests that policy change can help people form healthier habits, and the hope is that the government will act on this initiative to reduce childhood obesity rates by 50% by 2030. ◆

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Nearly 5.4 Million Cancer Survivors Experience Chronic Pain

CHRONIC PAIN, ONE OF the most common long-term effects of cancer treatment, is associated with lower quality of life, lower adherence to treatment, and higher healthcare costs. According to a new research letter, as the number of cancer survivors continues to grow rapidly in the United States, 5.39 million cancer survivors experience chronic pain.

In a study published in *JAMA Oncology*, investigators reported that about 1 in 3 cancer survivors reported having chronic pain. One in 6 reported experiencing high-impact chronic pain that restricts daily functioning, representing 2.51 million survivors. According to the investigators, these rates are nearly double that of the general population, which suggests the presence of unmet needs among the survivorship community.

These rates were determined from data extracted from the National Health Interview Survey from 2016 to 2017. The investigators identified 4526 cancer survivors from 59,770 survey participants. Among these survivors, 1648 (34.6%) reported having chronic pain; 768 (16.1%), high-impact chronic pain.

There were no significant differences in the prevalence of chronic pain or high-impact chronic pain based on age, sex, marital status, or region. However, there was a higher prevalence of both chronic and high-impact chronic pain among survivors with less than a high school education (39.2% for chronic pain, 18.5% for high-impact chronic pain), low household income (44.6% and 22.8%, respectively), public insurance for those aged 18 to 64 years (43.6% and 27.1%, respectively), and no paid employment (38.5% and 20.4%, respectively).

"Because socioeconomic status and employment are associated with insurance coverage and access to care in the United States, the patterns of chronic pain that we observed in cancer survivors may be explained by barriers to cancer care and pain management, as well as by the type and extent of cancer treatment received," wrote the authors.

They noted that the absence of significant differences in pain based on sex contrasts with the general perception of higher prevalence of pain in women compared with men. This could be because of insufficient statistical power from the limited sample size or because cancer-induced pain in both sex groups might have diluted the relative difference, they wrote.

Across cancer types, the prevalence of chronic pain was highest among survivors of bone (54%), kidney (52.3%), throat-pharynx (47.9%), and uterine (44.5%) cancers. Prevalence of chronic and high-impact chronic pain did not significantly differ based on time since diagnosis. ◆

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CLINICAL UPDATES

Blinatumomab Reduces MRD Prior to HCT in Pediatric Patients With B-ALL

WHEN GIVEN PRIOR TO hematopoietic cell transplantation (HCT), blinatumomab reduces minimal residual disease (MRD) and results in favorable leukemia-free survival, toxicity, and overall survival (OS) in pediatric patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL), according to study results appearing in the journal *Blood Advances*.

The findings have important implications because patients undergoing HCT with MRD are often at significant risk of relapse, but it has been unclear how to best eliminate MRD prior to transplantation. Approaches that used chemotherapy have yielded mixed results and added toxicity, including infection and organ injury, which can delay or prevent HCT.

Blinatumomab, which is approved for patients with relapsed or refractory B-ALL or persistent MRD, is designed to recognize the lymphoid marker CD19 that is expressed by most B-ALL.

Out of 15 patients aged 0 to 21 years included in the study, 14 were MRD negative following treatment with blinatumomab. Prior to treatment, the median MRD level was 0.57% of the mononuclear cell compartment.

The majority (80%) of patients, who were recruited from 5 Foundation for the Accreditation of Cellular Therapy–accredited pediatric HCT centers, received a 28-day course of blinatumomab at 15 µg/m2 per day between 2016 and 2018. Two patients had their initial treatment cycle shortened in order to start HCT preparative therapy, and the remaining patients received 2 courses of the treatment for 66 days.

According to the authors, patients proceeded to definitive HCT therapy without delay, in some cases starting the myeloablative preparative regimen just a few hours after completing their blinatumomab infusion.

"In patients where the unrelated donor was not readily available, this approach provided the advantage of a low-toxicity therapeutic bridge while waiting for an alternative donor," wrote the authors.

All the patients had successful neutrophil engraftment in the expected time frame, with a median time frame of 19 days. At 1 year, OS was 93.3%, and there was no transplant-related mortality in the first 100 days.

"Because blinatumomab activates the immune system and can result in cytokine release syndrome, there is some concern that any lymphocyte activation prior to HCT could negatively influence donor engraftment or perhaps cause greater rates of GVHD [graft-vs-host disease]," wrote the investigators. "However, all patients successfully engrafted and overall rates of grades 2 to 4 acute GVHD and chronic GVHD were low, despite alternative donors being the prominent stem cell source."

In the 30 days following HCT, 1 patient experienced any significant HCT-related complication. Two (14.3%) of the 14 patients who became MRD negative experienced grade 2 or 3 acute GVHD, and 3 (21.4%) experienced extensive chronic GVHD.

Four patients experienced a relapse of CD19-positive ALL at a median time of 355 days post HCT, but all 4 successfully achieved subsequent remission following CD19 positive–direct therapy and sustained a complete response at the time of the report. ◆

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Investigators Identify Multiple Myeloma Treatment Patterns by Age and Region

WITH 40% OF PATIENTS with newly diagnosed multiple myeloma (NDMM) or relapsed/refractory multiple myeloma (RRMM) ineligible for clinical trials, outcomes in elderly or frail patients are unclear. What data are available suggest that these patients have poorer outcomes, which may be a result of using less-aggressive treatments or because they have comorbidities or poor tolerance to therapies.

An abstract presented at the 24th European Hematology Association Congress, held June 13 to 16, 2019, in Amsterdam, the Netherlands, evaluated real-world treatment patterns by region and age to better understand and address these issues.

The investigators used data from INSIGHT MM, a global, prospective, noninterventional, observational study. Patients were enrolled from 16 countries and followed prospectively for at least 5 years, with data collected at baseline and every 3 months.

The enrolled patients included 1495 with NDMM and 1263 with RRMM. More than half (56%) of those with NDMM and just less than half (46%) of those with RRMM were younger than 66 years, respectively; 33% and 35% were between 66 and 75 years; and 14% and 19% were older than 75 years.

In patients who had new diagnoses and were younger than 66 years or between ages 66 and 75, triplet therapies were the top 3 most common regimens, whereas doublets were more common (2 of the top 3) in patients older than 75 years. However, for each age group, across all regions, the most commonly used treatment was bortezomib, cyclophosphamide, and dexamethasone (VCd). In Europe, VCd was the most commonly used among patients 66 years and older, whereas bortezomib, thalidomide, and dexamethasone was used most for patients younger than 66 years. In the United States, bortezomib, lenalidomide, and dexamethasone was the most commonly used for all age groups.

A similar pattern emerged in patients with RRMM, with younger patients more likely to use triplet therapy compared with older ones. However, there is greater treatment heterogeneity in patients with RRMM, which the investigators attributed to the greater number of novel treatments available in the setting. Although the second and third most commonly used regimens varied greatly, there was consistency at the top: Lenalidomide and dexamethasone was most commonly used across all age groups in Europe and for patients 75 years or younger in the United States. Patients older than 75 years were most commonly prescribed carfilzomib and dexamethasone.

"Regulatory reasons may also contribute to the greater number of regimens for RRMM, as drugs are generally first approved in this setting before moving to NDMM," the authors noted. ◆

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MANAGED CARE UPDATES

USPSTF: Screen Those at High Risk for Pancreatic Cancer

THE US PREVENTIVE SERVICES Task Force (USPSTF) has kept its recommendation against screening everyone for pancreatic cancer, but for the first time said this does not apply to people with known genetic syndromes of family history of the deadly cancer. It's an important shift for the diagnosis of a disease that, while still relatively rare, is becoming a leading cause of cancer death in the United States as survival rates improve for other types.

USPSTF's August 6, 2019, recommendation of "D" for population-wide screening for pancreatic cancer, published in *JAMA Internal Medicine*,[1] means the evidence shows that screening in asymptomatic adults demonstrates moderate or high certainty of no net benefit or that harms will outweigh benefits. An accompanying editorial in *JAMA Surgery* states that this conclusion is not a surprise, given the potential for false-positive results and harms of treatment.[2]

This is the first update of USPSTF recommendations on pancreatic cancer screenings in 15 years. It is now the fourth-leading cause of cancer death, although it is the ninth most common cancer among women and the 10th most common among men.[3]

Pancreatic cancer typically produces no symptoms early on, so it's frequently caught in later stages, when surgery may no longer be possible. Thus, the 5-year survival for pancreatic cancer remains a dismal 9% overall, although the rate is 34% for localized cancer.[3]

With those statistics, why not screen everyone? As Ralph H. Hruban, MD, and Keith D. Lillemoe, MD, note in their editorial, even the most sensitive test (99% specificity) will generate a number of false positives when applied to the general population, leading to more testing and perhaps surgery.

Still, Hruban and Lillemoe found hope in the task force's acknowledgment that evidence for the usefulness of genetic biomarkers in pancreatic cancer is rapidly improving. "Populations with significantly increased risk can now be targeted for screening, greatly increasing their positive pretest probability," they write.

The Pancreatic Cancer Action Network (PanCAN) took note of critical language changes for people with high risk. "USPSTF has made an important change to its definition of the 'general population.' For the first time, the USPSTF has noted their recommendation does not apply to people with a known inherited genetic syndrome or strong family history of pancreatic cancer.

"Instead, they are encouraged to participate in surveillance programs at 'experienced centers, ideally under research conditions,'" according to the advocacy group's website.[4]

PanCAN took note of the recent update to National Comprehensive Cancer Network guidelines, which called for all pancreatic cancer patients to receive germline cancer screening. ◆

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CMS Proposes Bundled Payments for Radiation Oncology

AFTER MONTHS OF ALLUDING to an upcoming change, on July 15, 2019, CMS proposed implementing bundled payments for radiation oncology. The Radiation Oncology (RO) Model could come as soon as January 1, 2020, covering 17 different types of cancer.[1]

The RO Model would be regulated by the Center for Medicare and Medicaid Innovation. Under the model, CMS would make bundled payments to physician group practices, hospital outpatient departments, and freestanding radiation centers that would cover radiation therapy spanning a 90-day episode. The model would be mandatory in certain parts of the country to determine whether prospective site-neutral, episode-based payments could reduce Medicare costs and improve the quality of care. In the proposed rule, CMS wrote that the agency believes having a mandatory model will offer access to more complete evidence of the impact of the model.

The model would qualify as an advanced alternative payment model (APM) and a Merit-based Incentive Payment System APM and would have a performance period of 5 years, beginning either January 1 or April 1, 2020, and ending December 31, 2024. HHS Secretary Alex Azar first hinted in November 2018 that a mandatory payment model for radiation therapy was coming, saying that the administration was revisiting previously scrapped mandatory models in cardiac care and new and improved episode-based models in other areas, such as radiation oncology.[2]

CMS cited 3 reasons for the need for payment reform in radiation oncology: lack of site neutrality for payments, incentives that encourage volume over value, and coding and payment challenges.

"This patient-centric and provider-focused model would improve the quality of care cancer patients receive and improve patient experience by rewarding high-quality patient-centered care that results in better outcomes through a prospective, episode-based payment methodology," CMS said in a statement.[1]

The payments would be split into 2 parts: a professional component to cover services that may be provided only by a physician and a technical component to cover services not provided by a physician, including the provision of equipment, supplies, personnel, and costs related to radiotherapy services.

All 17 cancer types that would be incorporated in the model are commonly treated with radiation, make up the majority of cancer incidence, and have demonstrated pricing stability. These include anal, bladder, breast, cervical, colorectal, head and cancer, lung, pancreatic, and prostate cancers.

Following the announcement, organizations responded with praise for a value-based model in radiation oncology but caution over the model being mandatory. Paul Harari, MD, FASTRO, chair of the American Society for Radiation Oncology (ASTRO), said in a statement that the model "is a step forward in allowing the nation's 4500 radiation oncologists to participate in the transition to value-based care that improves outcomes for cancer patients."[3] He added that ASTRO will submit comments on the specifics of the model, including the requirements for certain radiation oncology groups to participate.

The Community Oncology Alliance released a statement voicing its concern over the mandatory model, writing that although it believes the model includes a much-needed policy proposal to implement site-neutral payments, it "has deep reservations and fundamental opposition to a proposed mandatory or 'required' CMS Innovation Center (CMMI) model."[4] ◆

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Produced by Jaime Rosenberg and Samantha DiGrande | Edited for clarity.

Sue Friedman, DVM, Executive Director of FORCE: Facing Our Risk Empowered

Why is it important for people to know more about genetic testing, especially those with a family history of cancer?

There are a lot of reasons why it's important to know this information, and one of the things that's been exciting coming out of this [2019 American Society of Clinical Oncology Annual Meeting], but also other conferences over the years, have been these new agents, known as PARP [poly (ADP-ribose) polymerase] inhibitors, that are really targeted therapies and they were designed specifically with *BRCA* mutations, although now they're looking at how they work in other mutations, as well.

Right now, these agents are approved for people with mutations and in some cases without mutations, for ovarian cancer and metastatic breast cancer. We're really excited because there's some data presented here about treated in pancreatic cancer in patients with inherited mutations. These studies are particularly exciting to FORCE, because we were part of the efforts to recruit patients and accrue for these clinical trials. So, watching the data mature and be presented and watching that they're every promising and hopeful is very exciting to us and it allows us to go back to the community and share that hopeful information with them.

Are there any misconceptions we can address regarding genetic testing and family cancer risk?

One of the biggest misconceptions that we see is that these genes don't affect men. And there was some research presented [at ASCO] about prostate cancer. That's another area where there is a lot of research. So, men with mutations, when they do get prostate cancer, they tend to get a more aggressive prostate cancer—it's more likely to be metastatic. And the agents that I mentioned before called PARP inhibitors, they're looking at them for metastatic prostate cancer in men with mutations.

Some of these men have inherited mutations—so they inherited it from their mother or father, and they can pass it on to their children. But some men get what's called acquired mutations. So, these mutations develop within their prostate cancer, and actually this can happen in all the different cancers, but when we're talking about prostate cancer then obviously, we're talking about men.

But there is just this real general impression that these genes don't affect men and I think part of that is you know, sometimes we refer to *BRCA1* and *2* as the breast cancer genes even though they're associated with other cancer risks and another term that people use is the "Angelina Jolie gene" because she's one of the most famous people who has a mutation. And that can lead to the misconception that these genetic mutations are not important to men and they are.

Another important thing for people to be aware of is that genetic testing isn't just about *BRCA1* and *2*, and it's not just about breast and ovarian cancer. I talked a little bit about pancreatic and prostate cancer. There are other hereditary cancer syndromes. There's a syndrome called Lynch syndrome that's associated also with colorectal cancer and endometrial and uterine cancer in women, as well as ovarian cancer.

So, it's important. And this is the type of information people will get when they see a genetics expert, and they can make sure the right test is ordered because many of these, what we call panel tests, test for a lot of different genes. They can make sure the right test is ordered based on someone's family history and they can help them interpret it correctly.

Neil Goldfarb, President and Chief Executive Officer, Greater Philadelphia Business Group on Health

How are employers viewing the changing landscape as we see more precision medicines come to market that require genetic and diagnostic testing? What are they doing to manage these new, ballooning costs?

I think employers still rely very heavily on their vendors, their benefit consultants, their PBMs [pharmacy benefit managers], specialty PBMs to advise them on these kinds of issues. And I think there's still some question about for some of the precision medicine strategies, are they going to be inflationary or cost saving, quality improving or really no enhancement of value. So, we have to really judge each new technology independently. And I think that things are shifting where employers are recognizing that yes, every technology needs to be evaluated in some sort of a value framework, whether it's by the employer, one of their vendors, or some value measuring institute.

I think it's still fairly early on and employers, what I do know is their willing to cover these technologies even if they're expensive, if they're going to significantly improve the patient experience or the patient outcome. It's going to then be a question of is the price reasonable for the outcome that's being delivered?

Iuliana Shapira, MD, Chief Medical Officer, Regional Cancer Care Associates (RCCA)

How have data analytics improved your revenue cycle?

Data analytics is a fabulous tool because by collecting data, we know at what point in the revenues cycles we have problems. So, we know if problems are at various stages and how to address those barriers. Is data analytics ready for prime time? It depends what data comes in. A way to scrub and curate the data as it relates to revenue cycle is needed. A lot of the problems we have in revenue cycle nowadays are handled by highly specialized individuals who have training in billing, coding, insurance verification, benefits verification, and other areas of the revenue cycle.

However, it would be fantastic if we could address with artificial intelligence and big data certain aspects of the revenue cycle, such as insurance verification. We collect insurance information at the first patient visit, but if in between the visits, in that time interval the patient changes insurance, we do not have a mechanism right now to capture that. I don't think artificial intelligence is ready to capture that right now. However, I know there are many software products and companies that are working diligently to improve that situation.

How is RCCA managing the higher cost of immuno-oncology drugs in value-based care?

First of all, there is an old myth that you should not give up on a patient until you've given them immunotherapy. We have more and more knowledge in the

literature that immunotherapies do not work in certain cancers, and that data is rapidly incorporated into our care pathways. There is a problem in giving immunotherapy to patients that have certain cancers with specific mutations because immunotherapy may actually worsen the patient's survival and may actually make that cancer more aggressive, in addition to the fact that immunotherapy, just like any other therapy, has side effects. When we take the brakes off of our immune system, our immune system starts attacking normal organs. So, that is a limitation of immunotherapy to patients.

Certain patients should not get immunotherapy because they already have an immune-mediated disease. So, their immune system is already [compromised]. Giving them immunotherapy might just stimulate that pathology that already exists. That's one way to mitigate costs associated with unnecessary immunotherapy. Following strict national guidelines of cancer care is very important.

The second important development in controlling the cost of immunotherapy has just happened, when Novartis agreed with one of the larger insurers in Germany to give the money back for immunotherapy that did not work in a patient. Novartis has a CAR [chimeric antigen receptor] T-cell therapy that has a cost of about $500,000 per patient, and Novartis agreed that if that patient dies, or his disease or her disease progresses within a certain time limit, they will give back the money to the insurance company. Obviously, that type of arrangement, a value-based arrangement, should be translated in the United States. We strongly believe that the patient should have a money-back guarantee when using medication.

In addressing the high costs of prescription medication immunotherapy and any other medications that are out of reach, we should not bankrupt the patient, and we should not bankrupt the system. If the drugs do not fulfill their promise, the money should be reimbursed to the patient and the insurer. This can happen because we as oncologists follow national standardized guidelines. So, if the promised drug is the drug that we use in the condition and under circumstances and we're approved to use the drug, if the drug doesn't do the job, the drug company has to reimburse the money. That's one way to reduce costs.

The second way is to provide price transparency. Patients have the right to know how much immunotherapy costs versus another immunotherapy. They have to know that upfront, not have a bill sent at the end of treatment. Price transparency ensures that the patients know the cost and they have options to choose among different medications that are recommended by their physicians. I think that these are 2 interventions—price transparency, choice, and money-back guarantee—that will ensure our healthcare doesn't go bankrupt with treatments that do not fulfill their promise.

Jeanne Tie, MBChB, FRACP, MD, Medical Oncologist and Associate Professor, Walter+Eliza Hall Institute of Medical Research.

You are working on a blood test that could detect early stages of cancer. How does the test work and how is it advanced beyond current tests that are already in use?

So, the CancerSEEK blood test is a combination of circulating tumor DNA analysis—so using genotyping in patients' blood—in addition to protein bar marker in the blood to detect 8 common cancer types. What we've shown is that this blood test can detect up to about maybe 70% to 80% of current, common cancer types that doesn't have available screening method.

What it offers is that because it is a simple blood test it is much less invasive than other screening tests such as fecal occult blood is for bowel cancer. The blood test can also locate the tumor type to top 2 location which will allow clinicians then to focus the subsequent investigation such as [computerized tomography] scan or gastropexy based on the blood test result.

Obviously, it is a proof of concept study, so it isn't until randomized trial can demonstrate in a general, noncancer population that this blood test can pick up cancer and compared to not doing the blood test, I don't think it's ready to be used in the clinic, but it is certainly a first step towards a very exciting era.

Lani Alison, BSN, MS-HCQ, PCMH, CCE, Vice President for Clinical Affairs, Regional Cancer Care Associates

How is innovation being used to improve quality metrics in oncology care?

Innovation is being used in many different ways. There's innovation at the patient forefront, and then there's also innovation in data. So, what I really deal with is pretty much data that is then translated into the practice, and we need to have evidence-based data in studies that is really written by innovation. When we have innovative patient assistance, for example, or innovative strategies to improve patient outcomes, this has really been very helpful. When we say, "So, is this an innovation, or is this what we have done before?" Innovation can be a new way of doing things from already proven tactics.

For example, care management. Care management was an innovation a few years ago, maybe 10 years ago, so we then improved it to care coordination. When we care manage patients, it's not only with a provider that has given the opportunity to care manage a patient, but also it goes beyond that to other providers that are also taking care of the patients. So, that is an innovation in the way we manage patients outside of the acute care facilities.

What types of questions do patients ask about oncology care pathways and treatment guidelines?

They always ask, "Am I getting the low-cost treatments/ therapies because I'm on this pathway? What does pathway really mean?" So, we educate the patients that it's an advantage for them, because those pathways have been researched, are actively being studied, and are actively being used by many, so there is evidence that this is better and it also gives them a reassurance if we educate them well that these are the therapies that actually are tested already, that you don't have to feel like you're a guinea pig or anything like that that. They would think because of the word "pathway" that doesn't really mean that because I'm getting the lowest cost, I'm getting the lowest type of regimen. It's like you're buying a cheaper bag versus a designer bag. So, we have to be able to educate our patients that that is not so.

How has the implementation of the Oncology Care Model allowed practices to better integrate palliative care, and what impact does that have?

The practice transformation plan, which is really the heart of the Oncology Care Model [OCM], requires that we provide a patient a 13-point Institute of Medicine care plan, and one of those is either survivorship care planning for patients whose trajectory is survivorship and end of life, and part of that is really when the patient actually understands that the cancer has progressed and then the conversation starts. RCCA's approach to this is it doesn't matter, as long as you have spoken to the patient about cancer therapy. It may not be the metastatic type.

But I think in any chronic disease, not just cancer, we should really have a conversation with the patient about advanced care planning. Who is the person's healthcare proxy? Because that is pretty much a non-threatening or not very uncomfortable [thing] to talk about. In my family, we have already spoken about that. So, the conversation is a little bit lighter rather than a patient who is already in palliative care or you're going to tell the patient we're going to start you on palliative care and they don't even have a healthcare proxy. It's a big challenge.

OCM has really paved the way. We use it as the standard of care for cancer because it requires that. In the OCM model, it is very difficult to succeed if you don't have end of life/palliative care that includes palliative care and hospice and actually bereavement as part of its services. We have to really think about the patient's outcomes, which include financial outcomes for the patients, as well as the total patient experience. It has to be part of that. If you start asking about their healthcare proxy, when the time comes, you just move along the conversation and say, "OK, Susie is your proxy, now we're going to think about your cancer has progressed. What is next?" So, then if the patient is in pain, we're going to talk about palliation. You really are informing the caregivers of the patient what could be [coming] next. So, it's not going to be such an uncomfortable conversation anymore. ◆

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