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Payment Reform Efforts to Support Cancer Care Coordination, Treatment Planning

The American Society of Clinical Oncology (ASCO) is proposing to profoundly reform payment for cancer care. ASCO's Patient-Centered Oncology Payment: Payment Reform to Support Higher Quality, More Affordable Cancer Care (PCOP) proposal marks a significant step towards value-based reimbursement, fundamentally restructuring the way oncologists are paid for cancer care.

The group believes improved quality and reduced spending are possible by providing "sufficient payment" to support a range of typically unreimbursed services, including payment for care coordination and treatment planning based upon appropriate testing. Furthermore, PCOP would meet the criteria of an Alternative Payment Model as defined in legislation Congress enacted in an effort to repeal Medicare's Sustainable Growth Rate formula.

"[PCOP] ensures that oncologists provide the highest quality of care by getting adequate time to review and apply new genomic-based targeted therapies and immunotherapies," says Dan Zuckerman, M.D., co-chair of ASCO's Payment Reform Implementation Workgroup, in a statement. "This model incentivizes the right care for the right patient at the right time—precision medicine with compassion."

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Obstetric Groups Still Don't Endorse Universal Use of NIPT, But Expand Access

Conventional screening for common aneuploidies remain the "most appropriate" choice for first-line screening for most women in the general obstetric population, according to a committee opinion published online June 26 by the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine. However, the groups say that noninvasive prenatal screening (NIPT) using cell-free DNA (cfDNA) methodologies offers "tremendous potential" as a screening method for fetal aneuploidy and that any patient, regardless of her risk status, may choose cfDNA analysis as a screening strategy for common aneuploidies (trisomies 13, 18, and 21).

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Central to ASCO's proposal is addressing inadequate payment or currently uncompensated time for services critical to managing a complex illness. As part of basic PCOP model, the workgroup says oncology practices commit to delivering evidence-based care—ensuring patients receive the most appropriate tests and treatments, while avoiding unnecessary expenses. In return, oncology practices receive four supplemental, non-visit-based payments to support diagnosis, treatment planning, and care management. These monthly payments risk reduction if practices fail to adhere to evidence-based guidelines. Services like Evaluation & Management, infusions of chemotherapy, and drug administration in the practice setting will remain billable under the Medicare Physician Fee Schedule. However, for financially more aggressive practices, additional consolidated and bundled payment models are proposed.

"Payments are clearly moving away from FFS and toward increasing ties to value. But it is also clear that the major overhaul of physician payment that is coming with [Medicare Access and CHIP Reauthorization Act of 2015] is very much a work in progress."

—Mark B. McClellan, M.D., Ph.D..

"The savings from adequate care management and consistent application of appropriate use criteria are expected to more than offset the increased resources provide[d] to practices," writes ASCO in the PCOP overview. "Conservative estimates indicate a net reduction of at least 4 percent in total spending for payers ... [but] various demonstration projects and studies in oncology suggest the savings potential is much greater."

PCOP Goes Further Than CMS' Oncology Care Model

ASCO's PCOP expands upon a previous draft payment reform model the group circulated last year and experts say, takes payment reform even one step further than the Centers for Medicare & Medicaid Services' (CMS) Oncology Care Model (OCM). OCM, a multipayer payment and care delivery model, was unveiled by CMS earlier in the year, but was criticized for keeping fee-for-service (FFS) payments in place.

OCM is based on the oncology medical home concept. Like PCOP, OCM would pay oncologists in part on a per-member, per-month basis, with overall payments tied to financial accountability or risk, as well as quality. Participating practices would receive a $160 per-beneficiary payment on top of Medicare FFS payments for a 6-month episode of care. Additional semi-annual performance-based payments would be made for meeting a set of quality measures.

The second part of the plan involves shared-savings payments based on benchmark spending targets. The oncology practice can share in the savings achieved, if they reduce costs more than 4 percent below the target price.

"Payments are clearly moving away from FFS and toward increasing ties to value. But it is also clear that the major overhaul of physician payment that is coming with [Medicare Access and CHIP Reauthorization Act of 2015] is very much a work in progress," writes Mark B. McClellan, M.D., Ph.D., director of the Health Care Innovation and Value Initiative at the Brookings Institution, in *ASCO Daily News*. "It may be time to celebrate progress on payment reform, but it is also time to get to work to ensure that what comes next will fulfill the promise of better care and lower costs."

Takeaway: While 2015 is shaping up to be a breakthrough year in payment reform for oncology care, it remains to be seen whether alternative approaches to oncology payment succeed in improving quality of care, while controlling skyrocketing costs. G2

Obstetric Groups Still Don't Endorse Universal Use of NIPT, *Continued from bottom of p.1*

NIPT has been hailed as a major breakthrough in bringing sequencing-based testing into routine care, given the speed it has been adopted into practice since its commercial introduction.

The new statement expands the use of NIPT, compared to a 2011 ACOG recommendation, which stated that cfDNA testing should not be offered to low-risk women and only used in high-risk women. Yet, the new statement still falls short of universally endorsing the test, citing the limitations of cfDNA screening performance and limited data on cost-effectiveness in the low-risk obstetric population. The groups say that more recent data shows the tests' sensitivity and specificity in the general obstetric population are similar to the levels previously published for the aforementioned high-risk population, but that more false-positive test results are reported owing to the lower prevalence of aneuploidy in the general obstetric population.

The recommendation recognizes that patient choice is paramount to screening method choice, and that to make an informed choice women should be counseled regarding the limitations and benefits of NIPT. Patient-clinician discussion should include alternative methods of testing, as well as the option to not test at all.

The recommendations acknowledge that cfDNA testing only screens for the common trisomies (not neural tube defects or ventral wall defects, which should be tested using maternal serum alpha-fetoprotein screening and ultrasound). It also calls for further counseling and diagnostic testing for women with positive results, as well as women with indeterminate results.

The groups recommend against cfDNA testing in patients with multiple gestations and against cfDNA testing for microdeletion syndromes, due to a lack of clinical validation.

Takeaway: While falling short of universal recommendation of cfDNA-based NIPT, professional groups say that regardless of individual risk, any informed woman can choose to have the test. G2

NIPT Detects Presymptomatic Cancers

Sequencing cell-free DNA (cfDNA) from maternal plasma for noninvasive prenatal testing (NIPT) may also enable accurate presymptomatic detection of maternal tumors during pregnancy, according to a brief report published online June 5 in *JAMA Oncology*.

Large parallel sequencing of cfDNA has been employed to detect copy number variations for both detection of fetal aneuploidy and tumor characterization. The Belgium-based researchers optimized a large parallel sequencing–based NIPT dataset and analysis, to assess common trisomies, as well as genome-wide discrimination of fetal and maternal segmental aneuploidies.

Analysis identified three aberrant genome representation profiles during NIPT assessment in more than 4,000 prospective pregnancies.

The three patients were referred for whole-body diffusion-weighted magnetic resonance imaging. An ovarian carcinoma, a follicular lymphoma, and a Hodgkin lymphoma were confirmed with subsequent pathologic and genetic investigations. The authors say the three cancers fall within the "expected" range based on population cancer incidence rates of 1 per 1000 to 2000 person-years in 20- to 40-year-old women.

"Given the current large scale implementation of NIPT to screen for fetal aneuploidies, it is surprising that there are not more reports of maternal cancers presymptomatically revealed by NIPT," writes lead author Frédéric Amant, M.D., Ph.D., from Katholieke Universiteit Leuven. "One explanation is that current NIPT analyses focus only on deviations of the viable trisomies 13, 18, and 21. However, our observations suggest that slight adaptations to NIPT analysis enabling the interrogation of (segmental) aneuploidies genome-wide could not only avoid false-positive assignment of fetal aneuploidy due to the presence of a maternal cancer but, more importantly, enable identification of the imbalances as cancer-derived anomalies."

Inside The Diagnostics Industry

Molecular Testing Making Strides in Melanoma Care

Unlike most other cancer types, rates of melanoma are increasing. Melanoma rates doubled between 1982 and 2011, according to data from the U.S. Centers for Disease Control and Prevention (CDC). When diagnosed early, melanoma is highly survivable, but survival rates for advanced, stage IV melanoma remain below 20 percent. As new therapeutic options enter the commercial market, it is hoped these survival rates will improve. According to the CDC, the annual cost of treating new melanoma cases is projected to nearly triple from $457 million in 2011 to $1.6 billion in 2030. Given the increasing cost of treating record numbers of melanoma patients with expensive new therapies, payers are particularly interested in identifying the subset of patients most likely to achieve clinical benefit from the treatment.

Academic centers like Vanderbilt University (Nashville, Tenn.) have initiated extensive molecular testing in patients with advanced melanoma. Jeffrey Sosman, M.D., director of Vanderbilt's melanoma program, tells *DTET* that using a next-generation sequencing (NGS) platform the medical center is testing 300 genes (including point mutations, deletions, and amplifications in expression levels).

"We are looking at a broad number of genes that are not all targetable right now, but hopefully, in the future we will use more and more of this information and it will tell us what treatment to give or not give," Sosman says. "I see that there will be a shift towards more intense molecular definition of tumors, possibly reaching the point where many patients are getting whole exome sequencing. But, there will probably be a pull-back after we learn from it, we will pick patterns that are most important in affecting treatment and outcomes and retarget genetic profiling in a less encompassing way."

While molecular testing has entered the clinical realm to target therapies to specific mutations, experts expect advanced laboratory testing to play a prominent role across the spectrum of melanoma care in the coming years—identifying those at risk for the condition, diagnosing the lesion, selecting treatment, and assessing prognosis for recurrence or metastasis.

Targeted Melanoma Drug Approvals

Since 2011, six new drugs have been FDA approved for the treatment of melanoma - three immunotherapies and three targeted therapies.

Targeted Therapies

Molecular testing has made greatest inroads into clinical care of melanoma patients in the area of targeting therapy based on tumor mutation analysis. Several targeted therapies have been approved by the U.S. Food and Drug Administration (FDA) and have shown promise in extending the lives of patients with advanced melanoma. Immunotherapy has similarly shown promise in patients with advanced melanoma, although research continues to identify biomarkers indicating which patients are more likely to see benefit from the therapy. New studies are showing that this molecular testing is both feasible to guide treatment decisions and gaining traction in actual practice.

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Somatic Gene Mutations in Melanoma	
Affected Gene	Estimated Frequency (%)
BRAF	37 to 50
CTNNB1	2 to 4
GNA11	1.2
GNAQ	1.3
KIT	2 to 8
MEK1	6 to 7
NF1	11.9
NRAS	13 to 25

Source: Adapted from My Cancer Genome

Melanoma Mutations Are Actionable - NGS studies have revealed a significant number of actionable mutations in patients with advanced melanoma. Researchers from Fox Chase Cancer Center (Philadelphia) conducted mutational analysis on 60 archived tumor samples from patients with high-risk and recurrent melanoma. They sequenced targeted regions of 50 cancer-related genes and identified 101 mutations in 25 genes. At the American Society for Clinical Oncology's (ASCO) annual meeting (Chicago; June 3-7) the researchers revealed that two or more mutations were uncovered in 43.3 percent of samples (n = 26), while 13.3 percent of studied samples (n = 8) had no identifiable genetic alterations. Of the identified mutations more than two-thirds (68.3 percent, n = 41) were potentially actionable mutations (BRAF, KIT, or NRAS) with commercially available drugs, while another 21 genes could be targetable with a compound in a clinical trial, the authors said.

Mutational Testing Adopted Quickly - Two studies presented at ASCO suggested that there is considerable use of BRAF testing in clinical care. In a retrospective analysis of Canadian patients diagnosed with stage IV melanoma between 2012 and 2014, investigators found the trend for BRAF testing has grown, but that a significant percentage of patients remain untested prior to their first treatment (43 of 125 patients in 2014). Furthermore, a "surprisingly high percentage" of patients with BRAF mutations are still treated with chemotherapy (nine of 34), rather than targeted treatments.

In a larger U.S. study, researchers from Flatiron Health (New York) found that testing patterns for BRAF mutations show "fast and stable" adoption with testing rates ranging from 85 percent to 88 percent from 2012 through 2014. Examination of medical records from 760 patients show similar rates of testing across U.S. geographic regions. In contrast to BRAF mutational analysis, testing for KIT and NRAS were "sparsely performed" over the same time period (overall testing rates of 14 percent and 7 percent, respectively).

Other Prognostic Markers

In addition to determining which therapies are likely to be most effective for a particular patient, clinicians are searching for prognostic information as to which patients are at highest risk of recurrence or metastatic disease. Currently prognostic assessment is "crude" and based on the thickness of melanoma tumors.

Predicting Metastasis Risk - A 31-gene expression profile test (GEP) can accurately identify high-risk disease in patients with melanoma tumors of intermediate thickness (T2/T3), independent of sentinel lymph node biopsy status or tumor ulceration. The validation of the DecisionDX-Melanoma GEP test (Castle Biosciences; Friendswood, Texas) was presented at ASCO. Based on gene expression levels, 555 patients' tumors were retrospectively classified as either low risk (Class 1) or high risk (Class 2) of distant metastasis. Current risk assessment utilizes nodal metastasis, which the authors note is an imperfect predictor.

The multicenter study found that classification as low risk was a significant predictor of distant metastasis free survival and overall survival. Across validation cohorts the

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GEP test identified more than 80 percent of those patients who were at risk of disease progression or death both overall in T2/T3 patients, as well as in a lymph node-negative subgroup that might typically mistakenly be considered at lower risk for metastasis. The company says that this test can complement conventional staging, particularly in patients with intermediate-grade lesions.

"Not only does the DecisionDx-Melanoma test accurately identify these high-risk patients that are missed by today's staging system, but it also identifies patients who are at very low risk of metastasis with a Class 1 designation," said Derek Maetzold, CEO of Castle Biosciences, in a statement. "These data provide further validation that DecisionDx-Melanoma is a clinically important tool to identify tumors of intermediate thickness that are at high risk of metastasizing."

Total Mutation Burden May Predict Outcomes - Researchers from MD Anderson Cancer Center (Houston) and Lion Biotechnologies (Tampa, Fla.) developed an algorithm to estimate total tumor mutation burden in cutaneous melanoma using genes assessed in two NGS panels. The Predicted Total Mutation Load (PTML) of the tumor correlated strongly with the actual whole-exome sequencing mutation load of each tumor in three datasets. Low PTML was defined as a score of 100 or less, while high PTML was over 100. High PTML significantly predicted both increased progression-free survival and overall survival among patients, including those treated with immunotherapy.

Inflammatory Markers May Also Be Tied to Outcomes - In cutaneous tissue there is an established link between tissue damage, inflammation, and cancer development. Furthermore, there is evidence that melanoma is immunogenic. Yet, the correlation between inflammatory mediators, immunosuppressive cells and clinical outcomes in melanoma patients is still a matter of intense research, according to a review published in March 27 in *Discoveries Journal*. In the article, the Romanian-based researchers say there is a prototype of intratumor inflammatory infiltrate associated with a good prognosis in melanoma. That infiltrate is composed of numerous T cells CD3+, Langerhans cells, few/absent B cells CD20+ and few/absent plasma cells. They say that circulating immune cells with activated or suppressor phenotype would give the physician a more detailed immune status of the patient.

"A panel of tissue/circulatory immune markers can complete the immune status, can add value to the overall prognostic of the patient and, as a result direct/redirect the therapy choice," write the authors, led by Monica Neagu, from University of Bucharest (Romania). "The future lies within establishing low-cost, affordable/available, easily reproducible assays that will complete the pre-clinical parameters of the patient."

While immunotherapies are FDA-approved for the treatment of melanoma, clinicians are awaiting identification of markers that will clarify the prognostic value of immune cells.

Risk Assessment

Comprehensive skin cancer prevention programs could prevent 20 percent of new cases between 2020 and 2030, according to the CDC. Yet, other than skin-protecting measures there are currently few means to assess an average individual's risk of melanoma.

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Family History Is Small Percent of Cases - Familial melanoma accounts for approximately 10 percent of all melanoma cases and even then a minority of these cases are attributable to a single genetic factor, CDKN2A (p16). Experts say that even with this known link to some hereditary melanoma cases, the clinical utility of genetic testing for hereditary melanoma families is debatable because CDKN2A status may not impact medical management in patients with melanoma and there are no standard medical management guidelines for the mutation. Genome-wide association studies have identified numerous low-risk alleles, but again, they have not been incorporated into any meaningful risk assessment tools.

Molecular Testing For Melanoma Diagnosis

Myriad Genetics' myPath molecular test can differentiate benign moles from malignant melanoma with greater than 90 percent accuracy, according to a study published online April 13 in the *Journal of Cutaneous Pathology (JCP)*. This objective test may aid diagnosis, particularly ambiguous cases.

Histopathologic evaluation is considered the gold standard for the diagnosis of melanocytic lesions. But studies have demonstrated that in approximately 15 percent of cases (225,000 skin biopsies annually) diagnosis is ambiguous when histopathology is used alone. Even among experienced dermatopathologists these cases can generate disparate conclusions.

"myPath makes certain you have the right diagnosis before going down an intensive treatment pathway," Loren Clarke, M.D., Myriad's medical director for dermatology, tells *DTET*. "It is not because of a lack of expertise, but even with renowned dermatopathologists two of them looking at the same sample can arrive at different conclusions. They are acutely aware of the problems with diagnosis in these 10 to 20 percent of cases. myPath takes the subjectivity out of the diagnosis."

myPath assesses 23 genes (including 13 genes with known immune function, one cell differentiation control gene, and 9 housekeeping genes that ensure adequate RNA expression for analysis) using quantitative reverse-transcription polymerase chain reaction. By applying a threshold value and weighting algorithm to analysis, the gene expression signature produces a score that differentiates benign nevi from malignant melanomas. In the *JCP* validation study, myPath was able to identify malignant melanoma with a sensitivity of 90 percent and specificity of 91 percent.

Myriad says that a separate study shows that providing physicians with results of the gene signature assessment modifies physician behavior and patient management recommendations in approximately a third of cases, independent of histopathology.

In a previously published study in the *Journal of Medical Economics*, Myriad found that use of the test in suspicious, but difficult-to-diagnose, pigmented lesions reduced costs by $1,268 per patient over 10 years, a savings of 8.3 percent after accounting for the cost of the assay (reportedly $1,500). The myPath test is currently available to about 120 dermatopathologists (and at no cost to the patient) as part of an early access program.

Risk Data Can Inform Prevention Efforts - New research that shows patients act on insights from genomic risk assessments is encouraging to melanoma prevention experts. Screening for common genetic risk factors for melanoma could increase preventive behaviors among individuals who are at increased risk for hereditary melanoma, according to a study published in February in the *Journal of Personalized Medicine*. As part of the Coriell Personalized Medicine Collaborative, participants received a personalized risk assessment based upon information related to their own self-reported family history of melanoma as well as a genetic risk variant showing a moderate effect size. The researchers found that participants with reported family risk of melanoma, personal genetic risk, or both risk factors were significantly more likely to increase skin cancer preventive behaviors compared to participants with neither risk factor.

Takeaway: Molecular testing is already informing treatment selection for melanoma patients with BRAF mutations. Over the next five years, experts expect advanced laboratory testing to further improve identification of those at risk for melanoma, determine who will benefit most from immunotherapy, and predict risk of metastasis.

New Antibody Test Can Definitively Diagnose Irritable Bowel Syndrome

A new blood test that incorporates two antibodies can diagnose diarrhea-predominant irritable bowel syndrome (D-IBS), according to a study published May 13 in *PLOS One*. For patients with chronic diarrhea, the test can noninvasively distinguish D-IBS from inflammatory bowel disease (IBD), eliminating the need for costly and invasive exploratory testing.

"Having an early diagnosis means patients can avoid years of invasive tests and visits to specialists," lead author Mark Pimentel, M.D., from Cedars-Sinai Medical Center in Los Angeles, said in a statement. "With these new blood tests, many patients will now be able to proceed right to therapy for their condition."

To date, diagnosis of IBS has been based on a "diagnosis of exclusion," the authors say, which has involved a "great deal of expense and morbidity to patients with IBS." Imaging, endoscopy, colonoscopy, and blood testing have been utilized to rule out alternative "organic" explanations for diarrheal symptoms. While celiac disease (CD) diagnosis has been "greatly enhanced" using serum tissue transglutaminase antibody, a marker has been lacking for definitive diagnosis of D-IBS.

"[Anti-CdtB and anti-vinculin] represent the first opportunity to make IBS a diagnosis of inclusion rather than a 'diagnosis of exclusion.'"

—Mark Pimentel, M.D.

Commonwealth Laboratories (Salem, Mass.) commercially launched the $199 IBSchek test during Digestive Disease Week 2015 (May 17-19; Washington, D.C.). The enzyme-linked immunosorbant-based assay detects the presence of two antibodies—anti-cytolethal distending toxin B (CdtB) and anti-vinculin. The antibodies are associated with alterations in the intestinal microbiota resulting from acute gastroenteritis, usually caused by a bacterial infection. Previous studies have tied resulting alterations from acute gastroenteritis to D-IBS based on breath testing, culture studies, and deep sequencing of small bowel microbial flora.

In the *PLOS One* study, researchers assessed circulating anti-CdtB and anti-vinculin antibody levels in patients with D-IBS based on Rome criteria (n=2,375), as well as patients with IBD (n=142), CD (n=121), and healthy controls (n=43). Participants with IBD and CD had histologic confirmation of chronic inflammatory changes in the colon or small intestine.

The researchers found that both anti-CdtB and anti-vinculin titers were significantly higher in D-IBS subjects compared to IBD and healthy controls, as well as patients with celiac disease, Crohn's disease, ulcerative colitis, and celiac disease. The area-under-the-receiver operating curves were 0.81 and 0.62 for diagnosis of D-IBS versus IBD for anti-CdtB and anti-vinculin, respectively. Specificity was lower for both tests' ability to differentiate IBS from CD. When optimizing the test (an optical density of 2.80 or more for anti-CdtB and 1.68 or higher for anti-vinculin) led to specificity, sensitivity and likelihood ratio of 91.6 percent, 43.7 percent, and 5.2, respectively for anti-CdtB, and 83.8 percent, 32.6 percent, and 2.0, respectively for anti-vinculin.

"[Anti-CdtB and anti-vinculin] represent the first opportunity to make IBS a diagnosis of inclusion rather than a 'diagnosis of exclusion,'" write the authors, some of whom have financial ties to Commonwealth, which exclusively licensed patent applications for the blood tests from Cedars-Sinai. "As a biomarker, measurements of anti-vinculin and anti-CdtB antibodies could help to identify D-IBS without excessive investigation and may help to target investigations in those where the test is negative."

Craig Strasnick, Commonwealth's chief operating officer, says that quantification of the downstream cost savings associated with use of IBSchek is forthcoming in a publication later this year, but that the per patient savings are "substantial." Additionally, he tells *DTET* that data validating IBSchek in IBS patients presenting with constipation or mixed symptoms is also forthcoming this year.

Takeaway: A new test that could definitively diagnose IBS could substantially cut costs associated with expensive and invasive workups traditionally used to rule out other causes of diarrheal symptoms.

Putative Loss-of-Function Variants More Common Than Thought

Sequencing the genomes of healthy people uncovered the presence of many more rare diseases than expected. More than three percent of the U.S. population may have a genetic condition compared to previous estimates of less than 0.02 percent, according to a study published June 4 in the *American Journal of Human Genetics*. The authors say this study shows that genome sequencing information can dramatically improve prediction of disease. Furthermore, they say the study demonstrates the feasibility of "iterative phenotyping."

"Today, we tend to deliver medical care based on the expected response of the average patient," said National Human Genome Research Institute (NHGRI) Director Eric Green, M.D., Ph.D., in a statement. "Eventually, we want to deliver medical care based on individual genomic differences that enable more precise ways to prevent and treat disease. These findings move us closer to that reality."

It is recognized that genome analysis reveals much higher levels of putative loss-of-function (pLOF) than true LOF estimates (800 versus 100 variants per person). pLOFs can include nonsense, frameshift, and splice site alterations. Understanding the clinical implications of pLOF is complicated in real-life sequencing scenarios, as bioinformatics solutions are not yet capable of delivering accurate predictions of pathogenicity. Efforts are further complicated by limitations in discovery of novel phenotypic associations due to the use of individuals selected for predefined phenotypes in most genotype-phenotype correlation studies.

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>
> —Eric Green, M.D., Ph.D.

"With the increasing use of next-generation sequencing technologies for predictive medicine, it is critical to be able to predict the consequences of pLOF, especially in individuals without preexisting clinical diagnoses," write the authors.

In the present study, the researchers sequenced the exomes of 951 participants of the ClinSeq cohort (aged 45 to 65 years). Consequences of pLOF variants were characterized using iterative phenotyping in which participants were invited to a follow-up clinic visit if a family history was insufficient to confirm or rule out a diagnosis. Sequencing data was filtered for pLOF variants in genes likely to cause a phenotype in heterozygotes (with an autosomal-dominant inheritance pattern).

After filtering for quality of the sequencing data, researchers identified an average of 100,664 variants per individual, with an average of 484 pLOF variants per individual. Further filtering for pLOF variants that were considered highly likely to cause a phe-

notype in the heterozygous state yielded 82 variants in 103 participants. Of the 79 individuals available for follow-up assessments, the overall yield of positive phenotypes was 43 percent (n=34). For the 34 participants with findings or family histories that could be attributed to the variant, 28 variants were detected in 18 genes. An additional two participants had indeterminate findings (2 variants in 2 genes), while 43 had no personal findings and a negative family history for the trait (34 variants in 28 genes).

"For individuals without a clear family history of disease, variant identification and interpretation is more difficult because it is possible that the identified variant is not causative, and non-penetrance must always be considered."

—Jennifer Johnston, Ph.D.

"Although our positive predictive rate was 43 percent, it should be emphasized that these data altered the risk of a rare, autosomal-dominant disorder in these 79 participants from baseline (1/500 to 1/500,000) to approximately half," conclude the authors, led by Jennifer Johnston, Ph.D., from NHGRI. "Although it is true that not all of the phenotypes detected here are medically actionable, this study serves as a proof-of-principle that there might indeed be predictive value in healthy genomes and exomes, once our mutation prediction algorithms improve and broaden to encompass all genes and many mutations."

Of the 42 individuals who underwent follow-up phenotyping, 21 individuals (variants in 18 different genes) were negative on examination. Another 20 individuals with harmful mutations and a detectable phenotype upon examination didn't know they had a genetic condition. These conditions ranged from mild to potentially serious. Some of the findings included:

- Mild features such as short digits with a HOXD13 variant; deafness with a KCNQ4 variant; dystonia with a SGCE variant; and blistering of the feet with a KRT16 variant.
- Three variants resulted in biochemical phenotypes of protein S, factor XI, or TNFRSFB, but LOF variants in these genes are often non-penetrant for severe disease features.
- Some undiagnosed phenotypes with a more significant risk of morbidity and/or mortality to participants, but typically with later onset, included lipodystrophy with a PPARG variant; decreased lung function with a SFTPC variant; and left ventricular non-compaction with a MYH7 variant.
- Nineteen participants had variants in genes previously identified cancer susceptibility variants (BRCA1/2, FLCN, MSH6, PMS2, RAD51D, SDHC, XRCC2), but only six of these individuals had a clear family history of the associated cancers.

"For less-severe phenotypic features that might be present but underdiagnosed in the general population, such as hearing loss, confirming the causation of the variant is difficult and over-interpretation is possible," write the authors. "For individuals without a clear family history of disease, variant identification and interpretation is more difficult because it is possible that the identified variant is not causative, and non-penetrance must always be considered."

Fifteen identified variants were in genes on the American College of Medical Genetics and Genomics' list of genes to be considered for return of incidental findings. pLOF variants in these genes were identified in a total of 23 individuals, 16 of which were evaluated for phenotypic features. Seven of the 16 were positive for associated phenotypic findings and/or positive family history, while nine individuals did not have associated phenotypes or a positive family history. The researchers say

determining whether these individuals are nonpenetrant versus the variant being non-causative is "crucial" in the decision to return these variants.

Takeaway: While this study adds to the hope that genomic information can be used predictively, much more needs to be understood about the nature of penetrance and causative nature of genetic variants. G2

Cancer Screening Based on Unprovoked Venous Thromboembolism

A limited cancer screening strategy, including basic blood testing without a CT scan, is adequate for detection of occult cancer in patients with a first unprovoked venous thromboembolism (VT), according to a study published June 22 in the *New England Journal of Medicine*. An unprovoked VT (as opposed to a deep-vein thrombosis or pulmonary embolism tied to a transient risk factor like trauma, surgery, prolonged immobility, or pregnancy) may be an early sign of cancer. Previous studies estimate that as many as 10 percent of patients with an unprovoked VT receive a cancer diagnosis in the year following VT and unprovoked cases represent more than 40 percent of all VTs. Clinicians and payers have struggled with how aggressively to screen for occult cancers in these patients with unprovoked VT.

In the current multicenter, Canadian trial, researchers randomized 854 patients with a new diagnosis of first unprovoked symptomatic VT to receive either limited occult cancer screening (including medical history, physical exam, complete blood counts, serum electrolyte and creatinine levels, liver-function testing, and a chest x-ray) or extensive screening with the addition of a CT of the abdomen and pelvis. Additional sex-specific testing (mammography, Papanicolaou, and prostate-specific antigen) occurred for those not up-to-date with recommended screenings.

> *"The risk of subsequent cancer was also quite low, and 'doing more' did not lead to earlier cancer detection."*
>
> —Alok A. Khorana, M.D.

The investigators found that following the initial screening strategy, just over 14 percent of patients in both groups underwent additional testing for a potential cancer diagnosis. A total of 3.9 percent of all patients were diagnosed with cancer within 1-year of randomization, with no significant difference in numbers diagnosed between the groups—a lower than expected rate. Of patients over the age of 50 years, 6.7 percent in the limited-screening group and 10.2 percent in the extensive screening group underwent colon cancer screening (fecal occult-blood testing, sigmoidoscopy, or colonoscopy), which led to diagnosis of three colorectal cancers in the extensive screening group.

Limited screening missed four of 14 occult cancer cases, while extensive screening missed five of 19 occult cancer cases. Acute leukemia (two cases), gynecologic tumors (two), and colorectal tumors (two) were equally missed by the two screening strategies. The mean time to cancer diagnosis was similar between the strategies (4.2 months for limited versus 4.0 months for extensive screening).

"The risk of subsequent cancer was also quite low, and 'doing more' did not lead to earlier cancer detection," writes Alok A. Khorana, M.D., from the Cleveland Clinic (Ohio), in an accompanying editorial.

Takeaway: The risk of diagnosis with an occult cancer in the year following an unprovoked VT may be lower than previously thought, particularly among patients in their 50s. A limited cancer screening strategy is adequate to catch cancers in this population. G2

G2 INSIDER

Electronic Pop-Up Message Can Cut Nondirected Testing for Rare Conditions

A simple electronic decision support tool can reduce unnecessary testing conducted as part of nondirected assessments. A pop-up screen in electronic ordering systems significantly reduced testing for rare conditions commonly included with nondirected testing for liver disease, according to a research letter published June 1 in *JAMA Internal Medicine*. The researchers say this intervention is likely applicable in other clinical scenarios.

Elevated liver enzymes are estimated to affect nearly eight percent of the U.S. population. Resulting workups often test for viral hepatitis as well as Wilson disease, an inborn error of copper metabolism that affects 0.003 percent of the U.S. population and rarely presents with late onset. Initial Wilson disease diagnosis occurs based on ceruloplasmin blood levels.

In the current study, researchers evaluated the effect of a decision support tool on ceruloplasmin test utilization by measuring use rates seven months before and after implementing an electronic pop-up in the electronic medical record system at Beth Israel Deaconess Medical Center (October 1, 2013 through November 27, 2014).

Ceruloplasmin was ordered 448 times (mean times per day, 2.12) before implementation of the electronic pop-up. The researchers found that after implementation orders significantly dropped to 219 (mean times per day, 1.04). For comparison sake, the researchers assessed test orders for α1-antitrypsin, which is also commonly ordered to assess liver disease. Over the same time period there was no significant change in the rate of α1-antitrypsin orders (449 before and 418 after). The researchers also noted significant drops in simultaneous testing of ceruloplasmin and viral hepatitis (407 before versus 185 after implementation), as well as a significant reduction in ceruloplasmin testing in patients older than 55 years (158 tests ordered versus 61). Similarly the control rate of α1-antitrypsin test orders did not change in older patients. No cases of Wilson disease were identified.

"Further study is needed to extend this intervention into systematic changes including reflex testing of rare conditions after common diseases have been excluded or restricting testing options for clinicians," write the authors led by Elliot Tapper, M.D., from Beth Israel Deaconess Medical Center in Boston. "The findings from our study could inform programs to reduce the number of orders for nondirected tests in other common clinical scenarios, including antibody tests for [rheumatic] or infectious diseases or routine blood tests for routine daily blood tests for inpatients."

Company References

American College of Obstetricians and Gynecologists 202-638-5577

American Society of Clinical Oncology 571-483-1400

Castle Biosciences 281-796-9032

Centers For Medicare & Medicaid Services http://innovation.cms.gov

Commonwealth Laboratories 978-599-1380

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