G2 INTELLIGENCE
A DIVISION OF PLAIN LANGUAGE MEDIA

DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

January 2019

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Big Data Can Reshape Lab Reference Values in the Era of Personalized Medicine

As might be expected, there are substantial differences in "normal" laboratory values determined by healthy outpatients and critically ill patients in the intensive care unit (ICU). However, even among ICU patients, there are significant differences in the distribution of laboratory values for patients with the best and worst outcomes, according to a study published Nov. 9 in *JAMA Network Open*. The authors say that big data enables stratification of laboratory reference ranges by populations, clinical context, and even outcomes, which can lead to a fundamental shift in interpretation of laboratory results.

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Most Oncologists Report Using Sequencing-Based Panels In Practice

The majority of U.S. oncologists report using next-generation sequencing-based (NGS-based) tests to guide patient care, according to a study published Nov. 13 in *JCO Precision Oncology*, although use varied by clinicians' practice characteristics.

There has been some concern that the rapid pace of development of new commercial tumor gene sequencing panels has overwhelmed clinicians making it difficult for them to effectively incorporate new tests into routine patient care, given the volume of available tests, the scant data on their clinical utility, and the limited incorporation of such tests into evidence-based clinical guidelines.

Researchers used data from the National Survey of Precision Medicine in Cancer Treatment (February through May of 2017). The mailed survey was sent to a nationally representative sample of oncologists, with 1,281 of 3,378 participating. The National Cancer Institute, the National Human Genomic Research Institute, and the American Cancer Society sponsor the survey.

Most responding oncologists were male (66.4 percent) and white (62.6 percent). Less than one-third of respondents (31.1 percent) were in the 40- to 49-year age range. Geographically, about 10 percent of

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"The concept of one reference interval for all might need to be redefined," write the authors led by **Patrick Tyler**, M.D., from Beth Israel Deaconess Medical Center (Boston, Mass.). "While our simple model represents only a static snapshot of a dynamic situation, this effort represents the first attempt to generate a personalized, data-driven strategy for laboratory value interpretation based on clinical context and outcomes."

Tyler and colleagues used data from the Medical Information Mart for Intensive Care database (Jan. 1, 2001, through Oct. 31, 2012), which collects patient data for all ICUs at a large tertiary medical center in Boston. The researchers identified 38,605 ICU patients over the study period (56.6 percent male; mean age, 74.5 years) and compared the hospital's laboratory reference interval with one generated from data from patients in the ICU. Further, associations between laboratory values of ICU patients and outcomes (including mortality and length of stay) were evaluated.

Analysis focused on clinically relevant laboratory values, including minimum for albumin, ionized calcium, hemoglobin, and platelets; maximum for lactate; and both minimum and maximum for bicarbonate, blood urea nitrogen, creatinine, calcium, magnesium, phosphate, potassium, sodium, glucose, and white blood cell count. Albumin was ordered for 41 percent of patients, free (ionized) calcium for 50 percent, and serum lactate for 60 percent, while all other laboratory tests analyzed were ordered for more than 80 percent of patients.

The researchers found that hospital laboratory reference intervals were significantly different for ICU patients for all laboratory tests analyzed. The probability distributions of laboratory test values between the best and worst outcomes in ICU patients were all also significantly different from each other, with most laboratory tests having less than 0.8 overlap with the reference interval and about half of them having less than 0.5 overlap.

"By using data from ICU populations with high-resolution features and various outcomes, including both long term (e.g., survival) and intermediary (e.g., occurrence of arrhythmia), we can more accurately reference a patient against an outcome of interest, rather than with respect to a healthy population," write the authors. "This enhancement will, with further research … help us better understand how different laboratory values should be interpreted. Using a fixed reference interval for critically ill patients may not be the most effective strategy; rather, probabilistic interpretation of laboratory values may be more valuable in guiding treatment decisions and prognostication."

The authors say they realize that modifications of ranges would add complexity to the process of establishing and calibrating normal ranges, but in an era of big data and precision medicine, it "makes sense" to use available data "to increase the precision of what we do clinically."

Takeaway: Big data may reshape the way laboratory reference values are calculated and interpreted by incorporating clinical context and outcomes to the definition of normal.

DTET

Diagnostic Testing and Emerging Technologies (ISSN 2330-5177) is published by G2 Intelligence, Plain Language Media, LLLP, 15 Shaw Street, New London, CT, 06320.
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Fax: 855-649-1623
Web site: www.G2Intelligence.com.

Low-Value, Blood Glucose Self-Monitoring is Common

A substantial percentage of patients with type 2 diabetes may be inappropriately self-monitoring blood glucose, according to a research letter published Dec. 10 in *JAMA Internal Medicine*. Despite recommendations to the contrary, nearly one in seven patients with type 2 diabetes, but not using insulin, filled three or more claims for test strips over a one-year period. Interventions, the authors say are needed to curb this low-value testing.

Using claims data (Jan, 1, 2013, through June 30, 2015), from the Clinformatics Data-Mart Database (OptumInsight), the researchers identified 370,740 individuals (182 042 women; mean age, 68.5) who had two office visits less than 181 days apart, or either one emergency department visit or one hospitalization with a diagnosis of type 2 diabetes. Patients were followed for at least one year after filling a prescription for test strips, but were excluded if they received any prescription for insulin. Three or more claims for test strips were used to define routine testing.

The researchers found that less than one-quarter of patients (23.4 percent) filled three or more claims for test strips over the one-year timeframe. More than half of these individuals (51,820 of 86,747 routine testers) were potentially testing inappropriately, given that 32,773 individuals were taking agents not considered to be a risk for causing hypoglycemia (e.g., metformin hydrochloride) and 19,047 had no claims for any antidiabetic medications.

These 51,820 potentially inappropriate testers used a median of 2.0 strips per day, with median claims cost for test strips of $325.54 per person per year. The mean consumer copayment for test strips was $18.14 annually.

While the authors, led by **Kevin D. Platt**, M.D., from University of Michigan, Ann Arbor, warn that they although they were unable to account for changes in medications, lifestyle, or transient episodes of hypoglycemia that might warrant monitoring, they believe "strategies to improve engagement among clinicians and to educate patients are warranted to reduce low-value care." They suggest clinician-facing strategies might include clinical decision support in electronic medical records that create an alert when ordering test strips for patients who are taking nonhypoglycemic medications.

Takeaway: Efforts are needed to curb low-value, self-testing of blood glucose among patients with type 2 diabetes—particularly those who are not taking antidiabetic medications.

Pre-Op Urine Screening Not Necessary

Routine preoperative urine screening offers no clinical benefit, according to a large study published Dec. 12 in *JAMA Surgery*. Treating asymptomatic bacteriuria detected by screening does not cut the risk for postoperative infections, including UTI and SSI, the authors say.

"This study is the largest and most robust investigation into urine culture screening to date," write the authors led by **Jaime Gallegos Salazar**, M.D., from the VA Boston Healthcare System in Massachusetts. "It provides strong evidence that preoperative screening may not be valuable and should be discontinued as routine clinical practice."

Given concerns about antibiotic stewardship, the Choosing Wisely campaign recommends not treating asymptomatic bacteriuria (ASB) in most circumstances. However, surgeons installing new hardware often feel compelled to treat any colonizing organism in the hopes of preventing dangerous postoperative infections, such as prosthetic joint infections. More recently, the Infectious Diseases Society of America's 2018 AMB guidelines also recommend against preoperative screening, but lacked high-quality, supporting data.

The Veterans Affairs (VA) researchers used data from 68,265 U.S. veterans (96.2 percent men; mean age, 64.6 years) who underwent cardiac, orthopedic, or vascular surgical procedures at 109 U.S. Department of Veterans Affairs health care system facilities (Oct. 1, 2008, to Sept. 30, 2013). Associations between detection and treatment of preoperative ASB and postoperative outcomes, including surgical site infection (SSI) and urinary tract infection (UTI), were evaluated. Facility and/or surgeon practice guided the decision to screen with a preoperative urine culture. A positive culture was defined as 105 or more colony-forming units of any bacterial organism isolated.

The researchers found that preoperative urine cultures were performed in 26 percent of patients. Positive results occurred in 4.3 percent of screened patients, of which the vast majority (81.7 percent) were classified as having asymptomatic bacteriuria (ASB). Odds of SSI and UTI were similar for patients with and without ASB, even when adjusting for age, American Society of Anesthesiologists class, smoking status, race/ethnicity, sex, and diabetes status. Further, antimicrobial therapy targeted against the asymptomatic uropathogen was not associated with improvement in SSI or UTI.

Among patients prosthetic joint infection, there were no cases where the ASB organism matched the organism found in the joint infection. ASB organisms matched a postoperative wound culture (Staphylococcus aureus) in just cases.

"These findings will be greeted with joy by infectious diseases physicians far and wide," wrote **Barbara Trautner**, M.D., Ph.D., from Baylor College of Medicine in Houston, Texas, in an accompanying editorial. "Eliminating routine preoperative urine cultures will reduce the number of positive urine culture results in asymptomatic patients, in turn reducing unnecessary antibiotic use."

Takeaway: Routine preoperative urine culture screening should be discontinued among patients undergoing cardiac, orthopedic, or vascular surgical procedures.

SPECIAL FOCUS

Evidence Building for Use of Liquid Biopsy to Drive Treatment Decisions, Monitor Disease Activity

Emerging evidence shows that liquid biopsy is a viable option for detecting and monitoring genomic mutations to inform treatment decisions and to assess disease activity in real-world clinical settings.

Among the technology's many hopes is that it can inform genetic inquiries when tissue biopsies are not safely feasible, that it has the sensitivity to detect changes in resistance and disease burden before imaging modalities, that it can overcome the sampling challenge of tumor heterogeneity, and that eventually, the technology will enable pan-cancer screening for earlier disease detection.

Despite the promise that liquid biopsy can provide valuable clinical information in a minimally invasive manner, experts caution that the evidence base remains incomplete to warrant widespread clinical adoption of blood-based applications of next-generation sequencing (NGS) in cancer care.

The FDA has approved the CellSearch system (Menarini-Silicon Biosystems) for clinical use in testing for circulating tumor cells in cancer patients, the ability to detect circulating tumor cells, particularly in low-volume samples, remains a concern. Some experts are more encouraged about the prospect for adoption of sequencing technologies that can analyze circulating tumor DNA (ctDNA), even though estimates are that tumor-derived cfDNA accounts for less than 1 percent of total circulating DNA.

There is early evidence supporting the potential for liquid biopsy modalities to inform treatment of lung, melanoma, breast, ovarian, cervical, and bladder cancers. But currently, availability of tests outpaces the data supporting their use. *DTET* examined some recent studies providing valuable evidence supporting early clinical adoption.

Driving Targeted Therapy in Lung Cancer

Plasma NGS genotyping is feasible, rapid, and useful in the real-world clinical practice setting for patients with advanced non-small cell lung cancer, according to a prospective study published Nov. 28, 2018 in the *Journal of the National Cancer Institute*. A variety of oncogenic drivers can be identified from plasma ctDNA that can drive treatment decisions (e.g., targeted treatment) more quickly than tissue-based sequencing.

"We have shown that plasma-based ctDNA NGS assays allow for rapid and noninvasive genotyping that could immediately guide precision therapy, providing an important supplement to tissue NGS, as well as an important alternative when tissue biopsy is not feasible," write the study authors.

Researchers in the United States and Australia performed NGS targeting 21 genes in ctDNA from plasma samples of 210 patients with advanced non-

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small cell lung cancer. A subset of 106 patients had concurrent tissue NGS testing using a 468-gene panel. Most patients (81.4 percent) had previous conventional molecular testing for EGFR, ALK, and ROS1 mutations. The laboratory-developed test, ResBio ctDx-Lung assay (Resolution Bioscience), was used to evaluate plasma samples and the hybridization capture-based MSK-IMPACT assay (Memorial Sloan Kettering) was used for tissue-based genotyping.

Using ctDNA, the researchers detected somatic mutations in just under two-thirds of patients (135 of 210). Plasma NGS genotyping identified actionable driver mutations that led to a match with targeted therapy and clinical response in 46 of the 135 patients with identified mutations (EGFR, ALK, MET, and BRAF). As might be expected, ctDNA detection of mutations was significantly lower in patients who were on systemic therapy at the time of plasma collection versus those who were not (42.9 percent versus 75.0 percent).

"A driver alteration identified by plasma NGS can immediately direct clinical care."

— Joshua Sabari, M.D.

The median turnaround time for plasma NGS results was significantly shorter than for tissue NGS (9 versus 20 days). In 60 of the 105 patients who had concurrent plasma and tissue NGS, 56.6 percent of patients had at least one identical genomic alteration identified in both tissue and plasma. Among patients who tested plasma NGS positive, 89.6 percent were also concordant on tissue NGS. For patients who tested tissue NGS positive, 60.6 percent were also concordant for plasma. More specifically, for patients who tested plasma NGS positive for oncogenic drivers, tissue NGS concordance was 96.1 percent.

"A driver alteration identified by plasma NGS can immediately direct clinical care," write the authors led by **Joshua Sabari**, M.D., from Memorial Sloan Kettering Cancer in New York. "However, a negative result requires further investigation. Based on our findings, plasma NGS genotyping is best performed at initial diagnosis in conjunction with tissue biopsy and at the time of clinical or radiologic progression, as the yield of ctDNA might be highest at those times based on its correlation with tumor burden."

Monitoring Melanoma Activity

Assessing ctDNA can provide evidence of melanoma activity before it is detectable on imaging, according to a study published in the October issue of *Molecular Oncology*. The authors say this improves the current standard of care, particularly in melanoma patients, in whom the disease can metastasize to unusual sites.

The researchers prospectively enrolled patients into three cohorts. The first group had 60 patients with radiographically measurable metastatic melanoma. The second group of 29 patients had surgically removed high-risk (stage IIB-IV) melanoma whose tumor tissue revealed any of the seven common mutations. The third group included 30 patients who were receiving or had received

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Germline Mutations Detectable in ctDNA

A separate, small study published in Endocrine Practice in September Putative germline mutations can be detected from cfDNA across multiple genes and cancer types without prior mutation knowledge, according to a study published Oct. 19 in the *Journal of Clinical Oncology*.

The researchers analyzed data from 10,888 unselected patients with advanced cancer (lung, 41 percent; breast, 19 percent; colorectal, 8 percent; prostate, 6 percent; pancreatic, 3 percent; and ovarian, 2 percent. All patients underwent Guardant360 testing between November 2015 and December 2016. Samples were screened for 16 clinically actionable genes (APC, ATM, BRCA1, BRCA2, CDKN2A, KIT, MLH1, NF1, PTEN, RB1, RET, SMAD4, STK11, TP53, TSC1, and VHL) with known hereditary cancer associations.

The researchers identified 156 individuals (1.4 percent) with suspected hereditary cancer mutations in 11 genes. BRCA1 and BRCA2 mutations were the most common (78 percent combined). Of the 107 unique mutations, 82.2 percent were previously identified in ClinVar as likely pathogenic or pathogenic. Many mutations were detected in patients with cancers lacking clear guidelines for hereditary cancer genetic counseling and testing.

Putative germline mutations were more frequent in individuals younger than 50 (3.0 percent versus 1.2 percent in patients 50 years and older) and patients with ovarian (8.13 percent), prostate (3.46 percent), pancreatic (3.34 percent), and breast (2.2 percent) cancer. For the 12 patients with multiple samples, putative germline mutations were consistently identified.

"Incidental putative germline mutation reporting in these cancer types [where routine germline testing is not common] could significantly affect clinical care," write the authors led by **Thomas Slavin**, M.D., from City of Hope in Duarte, Calif. "Given the clinical significance of identifying hereditary cancer predisposition for patients and their families as well as targetable germline alterations such as in BRCA1 or BRCA2, research on the best way to validate and return potential germline results from cfDNA analysis to clinicians and patients is needed."

The authors caution that incidental cfDNA germline evaluation should not replace validated hereditary cancer gene testing, but could serve as an important supplement to increase the reach of genetic cancer risk assessment, especially in populations with more common germline founder mutations or in cancers without clear hereditary cancer genetic testing guidelines.

therapy and had any of the seven common mutations. All patients' plasma samples were evaluated with a polymerase chain reaction-based BEAMing (beads, emulsions, amplification, magnetics) assay (Sysmex Inostics) to assess mutational status (seven BRAF and NRAS somatic mutations), total tumor burden, and when appropriate, inform targeted therapy selection.

The researchers identified 260 plasma mutations with BEAMing across all three cohorts. In 60 patients who underwent both plasma and tissue testing, tumor tissue testing revealed one of the seven mutations of interest in nearly two-thirds of patients (38 of 60). In 33 of those 38 patients (86.8 percent), mutations identified in ctDNA exactly matched the mutations found in tissue samples, yielding a sensitivity and specificity of the ctDNA assay of 86.8 percent and 100 percent, respectively. As might have been expected, higher tumor burden and visceral metastases were associated with detectable ctDNA.

In the 29 patients with surgical removal of the tumor, five had recurrent melanoma during the study, which was detectable by ctDNA in two cases. Among the 30 patients receiving treatment, 17 responded to treatment. Among the 13 nonresponders, for four of those 13, CT scan and ctDNA results detected disease activity simultaneously. In four other cases, ctDNA results predicted disease progression that was later confirmed by imaging.

Interestingly the sensitivity of the BEAMing assay appears to be impacted both by disease burden and by loca-

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> *"Many technical hurdles have been resolved thanks to newly developed techniques and NGS analyses, allowing a broad application of liquid biopsy in a wide range of settings. ... Still application is far from reality but ongoing research is leading the way to a new era in oncology."*
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> — Raffaele Palmirotta

tion of the tumor, the authors say. ctDNA levels were not detectable in patients with only locoregionally recurrent disease in skin and lymph nodes. Further, metastatic disease confined exclusively to the lungs and/or brain often failed to produce detectable amounts of ctDNA.

"Our study results demonstrate that incorporating ctDNA assessments into real-world melanoma patient management can influence patient care decisions, alter radiographic interpretations, and impact clinical outcomes," write the authors led by **Steven Rowe**, M.D., Ph.D., from Johns Hopkins University in Baltimore, Md.

The Future of Liquid Biopsy

While the emerging evidence supporting the clinical use of liquid biopsy is promising, many unanswered questions remain. For instance, it is not yet clear how frequently plasma-based assessments of targetable somatic mutations are needed to improve patient outcomes, particularly when the mutation is not identifiable in tumor-based molecular testing and tumor growth is not apparent on imaging studies.

"Many technical hurdles have been resolved thanks to newly developed techniques and NGS analyses, allowing a broad application of liquid biopsy in a wide range of settings. ... Still application is far from reality but ongoing research is leading the way to a new era in oncology," writes **Raffaele Palmirotta**, from University of Bari Aldo Moro in Italy, in a review published Aug. 29, 2018 in *Therapeutic Advances in Medical Oncology*. "Large-scale and multicenter trials are also ongoing to confirm all the potentialities that are now being studied in order to fully define the exact settings and conditions for the application of liquid biopsy and confirm the comparison of performance with current solid biopsy methods."

Experts also say that financial data is lacking, including cost benefit analysis compared to conventional biopsies and imaging, evidence of improved outcomes, and the potential downstream costs (or savings) resulting from plasma-based NGS.

"For successful integration of plasma NGS into clinical practice, universal guidelines, both from an informatics and a technical standpoint, are essential and need to span multiple companies and institutions," writes Sabari and colleagues. "Not all assays are the same."

Takeaway: Evidence is mounting supporting plasma-based NGS for detection of genomic mutations in cancer patients. While the potential exists to apply the technology to screening, diagnosis, prognosis, and monitoring of disease, experts believe use of the technology to inform treatment decisions and to monitor disease activity are the applications closest to becoming a clinical reality.

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respondents reported practicing in a rural setting. Most respondents reported an affiliation with an academic institution. More than one half of respondents (56.3 percent) reported having some training in genomic testing. On average, respondents see 101 unique cancer patients each month.

> *"These results may reflect oncologists' use of NGS testing to inform treatment strategies when established therapies have failed or when there is uncertainty about the usefulness of existing treatment guidelines for less common clinical situations."*
>
> — Andrew Freedman

The researchers found that three-quarters of oncologists reported using NGS tests to guide treatment decisions. However, use differed according to the physician's demographic and practice characteristics. Use of NGS tests was more common among younger oncologists (less than 50 years of age), as well as those holding a faculty appointment, having genomics training, seeing more than 50 unique patients per month, and having access to a molecular tumor board.

NGS test results informed treatment often for 26.8 percent of respondents, sometimes for 52.4 percent, and never or rarely for 20.8 percent of oncologists. Of the oncologists who reported using NGS tests often in the past 12 months, 34.0 percent did so to guide treatment decisions for patients with advanced refractory disease, 29.1 percent to determine eligibility for clinical trials, and 17.5 percent to inform off-label use of Food and Drug Administration–approved drugs.

"These results may reflect oncologists' use of NGS testing to inform treatment strategies when established therapies have failed or when there is uncertainty about the usefulness of existing treatment guidelines for less common clinical situations," write the authors led by Andrew Freedman, from the National Cancer Institute in Rockville, Md.

The survey asked specifically about 11 commercially available NGS tests, including: CancerSELECT or Cancer Complete, Caris Molecular Intelligence or Target Now, CGI Complete, FoundationOne, FoundationOneHeme, FoundationACT, GPS Cancer, Guardant360, Omniseq Comprehensive, OnkoSight Tumor Panels, and ARUP Laboratories' Solid Tumor Mutation Panel. Multimarker gene-expression profiling (e.g., Oncotype DX for breast cancer) were not classified as NGS tumor tests. Among the 959 oncologists who ordered any of these NGS tests, past 12 month volumes were low, with 28.2 percent ordering one test, 31.7 percent ordering two tests, 23.3 percent ordering three tests, and 16.7 percent ordering four or more tests.

More than half of oncologists reported that NGS test results were difficult to interpret either often or sometimes. One-quarter said they referred patients to other providers for NGS testing, possibly suggesting a lack of expertise or comfort for ordering and interpreting NGS tests.

Takeaway: NGS-based tests are being used in clinical practice to inform treatment decisions for solid tumors. However, use varies by oncologists' personal and practice characteristics and seems to inform care particularly for more difficult cases.

Cytokines Could Predict Risk of Side Effects From Immunotherapy

Blood-based cytokine markers may help identify cancer patients at greatest risk of developing side effects from immunotherapy treatment, according to a pilot study published Oct. 31 in the *British Journal of Cancer*. Patients with lower pretreatment cytokine levels experienced greater increases in immune-related adverse events (irAEs), as did patients with greater post-treatment increases in some cytokine levels. The authors say these findings suggest that underlying immune dysregulation may be associated with higher risk for irAEs.

Estimates are that between 40 and 80% of cancer patients on immune checkpoint inhibitors develop immune-related adverse events (irAEs), some of which can be severe or permanent.

"Identifying these cytokines and other biomarkers for the prediction and tracking of autoimmune toxicity could help us customize immunotherapy, tailor monitoring and increase patient safety, and possibly even expand the use of immunotherapy to populations that are currently excluded," said senior author David Gerber, M.D., in a statement.

The need to identify patients at risk of AEs is great, given recent reports that side effects from certain immunotherapies may be more common than reported in the initial trials that led to the approval of these therapies. According to a study presented at the annual Palliative and Supportive Care in Oncology Symposium (Nov. 16-17; San Diego), analysis of real-world claims data from nearly 2,800 people with non-small cell lung cancer treated with immune checkpoint inhibitors experienced irAEs at rates substantially higher than in clinical trials.

Estimates are that between 40 and 80% of cancer patients on immune checkpoint inhibitors develop immune-related adverse events (irAEs), some of which can be severe or permanent. Diagnosis is challenged by the fact that irAEs can occur at any point in therapy and lack a specific diagnostic test.

In the pilot study, 65 patients receiving immune checkpoint inhibitors and 13 healthy controls were evaluated for 40 cytokines, markers of systemic immune status. Blood samples were collected from cancer patients at baseline, after one treatment cycle (either 2 weeks or 3 weeks), and at 6 weeks. Two samples were collected from healthy controls approximately two to three weeks apart.

The researchers found that irAEs occurred in 35 percent of cases overall. Specifically, irAEs occurred in 34 percent of patients treated with anti-PD1/PDL1 therapy and in 60 percent of patients treated with a combination of anti-PD1/PDL1 and anti-CTLA4 therapy. An irAE also occurred in the single patient treated with anti-CTLA4 monotherapy.

Cytokine levels were stable over time among healthy controls and lower than those in cancer patients at baseline. Patients who developed irAEs had lower levels of CXCL9, CXCL10, CXCL11 and CXCL19 at baseline and exhibited greater increases in CXCL9 and CXCL10 levels at post-treatment versus patients without irAEs.

"The incorporation of data from pre-treatment baseline and after 1 to 2 doses of checkpoint inhibitor therapy (before the onset of most irAEs) means that these or the related biomarkers could serve to guide patient manage-

ment in real time," write the authors led by Shaheen Khan, from University of Texas Southwestern Medical Center in Dallas.

The authors say that their next steps include a forthcoming multicenter clinical trial that will enroll 600 patients and include evaluations of 130 autoantibodies, genetic tests for genes associated with autoimmune and inflammatory diseases, and functional tests, including cytokines.

Takeaway: Cytokines may be effective as biomarkers for predicting the development of irAEs in cancer patients undergoing immunotherapy treatment.

Polygenic Risk Score Predicts Drug Efficacy with Schizophrenia

A polygenic risk score (PRS) may be able to predict response to antipsychotic drug treatment in patients with their first episode of psychosis from schizophrenia, according to a study published Nov. 5 in the *American Journal of Psychiatry*. Specifically, higher PRSs were associated with poorer treatment response.

""Polygenic risk scores represent the combined effects of many thousands of genetic variants across the entire genome, and better represent the very complex genetic nature of schizophrenia," said **Jian-Ping Zhang**, M.D., Ph.D., the study's lead author, in a statement. "These results suggest that polygenic burden may affect severity of illness, in addition to reflecting risk for developing psychosis."

> *"PRS represents the total genetic burden of liability to schizophrenia. Conceivably, higher genetic burden may implicate a broader range of etiopathophysiologic mechanisms, thereby rendering patients less responsive to drug treatment based primarily on a single mechanism of action (dopaminergic blockade)."*
>
> — Jian-Ping Zhang, M.D.

Despite adoption of targeted treatment in other clinical areas, prescribing in psychiatry remains largely a trial-and-error endeavor, with an estimated 40 percent of patients with schizophrenia failing to respond to common antipsychotic drugs.

In the present study, researchers chose patients with first-episode psychosis in order to minimize previous drug exposure and presumably increase the effect size of the genotype-phenotype association. Researchers used a discovery cohort of 77 patients from the Zucker Hillside Hospital First-Episode schizophrenia trial, as well as three validation cohorts—the European First Episode Schizophrenia Trial (EUFEST; n = 141), the Programa Asistencial Fases Iniciales de Psicosisde Cantabria, Spain (PAFIP; n = 192), and the Center for Intervention Development and Applied Research (CIDAR; n = 100).

The PRS was based on the Psychiatric Genomics Consortium schizophrenia genome-wide association study, which identified 102,636 single nucleotide polymorphisms. The PRS was calculated for each participant as the weighted sum of all risk alleles carried. Symptoms were measured using total symptom rating scales at baseline through week 12. Response rate defined as at least a 50 percent reduction in total symptoms scores.

The researchers found that higher PRS significantly predicted greater post-treatment symptoms in the combined replication analysis and was individually significant in two of the three replication cohorts. Patients with low PRS were more likely to be treatment responders compared to patients with high PRS (90 percent more likely to respond in the two Caucasian samples). In the low PRS group the response rate was 60.9 percent versus52.1 percent in the high PRS group. PRS was not significantly correlated with baseline total symptoms in any of the cohorts.

"PRS represents the total genetic burden of liability to schizophrenia. Conceivably, higher genetic burden may implicate a broader range of etiopathophysiologic mechanisms, thereby rendering patients less responsive to drug treatment based primarily on a single mechanism of action (dopaminergic blockade)," writes Zhang, from the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in New York. "As such, the PRS approach may be useful in both a practical and a theoretical sense in predicting clinical treatment response."

Future studies with larger samples may also result in the ability to identify a PRS cutoff with sufficient explanatory power to attain clinical utility.

Takeaway: PRS burden may have potential utility as a prognostic marker of treatment response in patients with schizophrenia.