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New Trends, Applications, and IVD Industry Analysis

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Report Finds Genetic Tests and Their Reimbursement Increasingly Complex

The health care technology company Concert Genetics (formerly NextGxDx; Nashville, Tenn.) recently released its third edition of *The Current Landscape of Genetic Testing*, a comprehensive report looking at the genetic testing marketplace, including trends in available tests and reimbursement.

The report is based on Concert Genetics' Genetic Health Information Network, a software and information technology platform that aims to enhance the transparency and efficiency of genetic testing for clinicians, hospitals, laboratories, and payers by enabling comparison between all available genetic test products, including laboratory developed tests, available on the market.

Increasing Number of Tests, Particularly Panels

The company's latest analysis shows that as of March 2018, the total number of genetic tests actively marketed by CLIA-certified U.S. laboratories was 74,448 genetic test units (GTUs; defined as any orderable combination of analytes and techniques at a specific point in time, sold as a single item in a laboratory catalog). On average, more than 14 GTUs per day are entering the commercial market—a pace faster than in previous high-growth years.

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Whole-Genome Sequencing Can Improve Blood Transfusion Matches

Antigen typing based on whole-genome sequencing (WGS) can enable more precise matching of blood transfusions, according to a study published online May 17 in *The Lance Haematology*. The authors say the 99 percent accuracy of their method, based on WGS and a validated computer algorithm, holds the potential to improve transfusion outcomes and transform the practice of transfusion medicine.

Most people know their A, B, AB and O (ABO) blood types, but there are more than 300 other red blood cell (RBC) antigens and 33 platelet antigens. Receiving a blood transfusion with non-matched antigens can trigger an immune response and lead to potentially deadly complications, particularly in patients needing multiple transfusions.

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Report Finds Genetic Tests and Their Reimbursement Increasingly Complex, *from page 1*

During the 12 months ending March 1, 2018, a net total of 801 new panels entered the commercial market at a rate of more than 15 genetic test panels per week. The new net total of panels in the last year represents more than 8 percent of the total number of panels (9,488) on the market, Concert Genetics says.

Continued testing growth, especially in multigene panel tests, is "compounding complexity" across the health care system—from test ordering through reimbursement. The company says that expansion in the number of genetic tests is outpacing ordering formularies, billing code sets, evidence of clinical utility, and coverage determinations. Providers are having difficulty differentiating tests, complicating ordering, and payers face confusion around payment integrity. Their inability to adapt policies to keep pace with test development is causing them to miss opportunities to harness the value of precision medicine, Concert says.

Concerts' analysis of claims data shows that coding for these panels varies widely. The company's data shows, for example, that in any given month, expanded carrier screening panels are billed 350 to 450 different ways. During the 18-month period from January 2016 through June 2017, these panels were billed cumulatively in more than 2,500 unique combinations—posing an administrative challenge for payers and other health system providers alike.

Not All Segments Growing, Reimbursed the Same

The number of pediatric and rare disease tests grew faster than any other clinical domain in 2017, Concert says, although there was "substantial" growth in test for the clinical areas of prenatal, cancer, hematology, and neurology.

The test types most commonly launched into the market in the past year do not correlate with the tests being paid for by commercial health plans, Concert Genetics writes in its report. Genetic tests in prenatal, hereditary cancer, and oncology treatment clinical areas represent roughly 90% of all commercial payments, but were not the fastest growing test segments in terms of number of new tests.

Based on the company's analysis of commercial health plan claims from tens of millions of commercially insured members, whole-exome sequencing, while growing in availability, is not frequently paid for by health plans, calling the total reimbursed volume "marginal." Specifically, the company shows, the maximum number of commercial health plan paid claims for the two billing codes specific to exome sequencing testing in any given quarter (2015 through 2017) was just 20—"a fraction of a percent of the hundreds of thousands of paid claims across all genetic testing" for this time period, although the company does acknowledge it is "likely" that some exome sequencing tests are being billed and paid under miscellaneous molecular CPT codes.

Takeaway: The number of commercially available genetic tests, particularly multigene panels, are growing substantially, but are contributing to greater confusion in the marketplace around test selection, coverage, and reimbursement.

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Markers Assess Risk of Preterm Birth, With or Without Preeclampsia

Preterm birth (PTB) is a growing problem in the United States and worldwide that has long-term consequences given the increased likelihood of long-term morbidities associated with PTB. To address this concern, there is increasing interest in the use of biomarkers to identify women at high-risk, who might benefit from treatment with existing therapies. Several tests are in development and nearing commercialization.

A study published May 24 in the *Journal of Perinatology* highlights the development of a comprehensive test for PTB across subtypes, including with or without preeclampsia. Initial trials show that combined with maternal age and poverty status, mid-pregnancy immune and growth factors reliably identified most women who went on to have a preterm birth (PTB) with or without preeclampsia.

Markers were tested in serum samples collected at 15 to 20 weeks into pregnancy as part of routine prenatal screening among women participating in the California Genetic Disease Screening Program. The makers' predictive performance was assessed in training and testing subsets. The identified women had singleton deliveries in California between 2009 and 2010, including 200 PTB, defined as gestational ages at birth less than 32 weeks and 200 term pregnancies. Detailed demographic and obstetric information available in a linked hospital discharge birth cohort database maintained by the California Office of Statewide Health Planning and Development. In total, 64 markers assessed using multiplex technology.

The researchers found that 25 target immune and growth factors (eight interleukins, one interferon, one factor from the TNFA super family, five chemokine ligands, five growth factors, two colony-stimulating factors, PAI1, resistin, and RAGE), along with maternal age above 34 years of age and low-income status were able to identify more than 80 percent of women going on to deliver preterm in the training set and 75 percent of women going on to deliver preterm in the testing set. The markers' best performance was in women with preterm preeclampsia.

"Although we contend that the currently presented algorithm represents an improvement over these other methods given that it focus on the commonalities across PTB subtypes and relies on widely available multiplex technology that allows multiple markers to be measured in a single test, it is critical to note that there are likely some benefits to focusing within subtypes," write the authors led by Laura Jelliffe-Pawlowski, from University of California San Francisco. "It may be that the present test could be improved further by the inclusion of, for example, a second-tier -omics-based test that addresses other protein-based or metabolic factors. .... Such an approach might allow for broad testing for baseline all PTB [with or without] preeclampsia risk and second-tier testing that is specifically aimed at early PTBs and preterm preeclampsia with a focus on term false-positive reduction."

Takeaway: Advances in understanding markers predictive of poor pregnancy outcomes may soon advance prenatal care.

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Lack of Utility Evidence Still Hampers Adoption of Pharmacogenomic Testing: Benefits Seen in the Field of Psychiatry

For years it had been hoped that pharmacogenetic (PGx) testing would be a leading application for personalized medicine, but adoption of PGx testing has not lived up to its potential and remains in an early stage of real-world use due to a lack of clinical evidence of utility and low provider awareness.

Particular interest was paid to tests that include the 13 genes included in the Clinical Pharmacogenetics Implementation Consortium's (CPIC's) guidelines.

It is recognized that genotype can impact the efficacy and/or toxicity of medications. The U.S. Food and Drug Administration (FDA) includes PGx considerations on the boxes of nearly 200 medications and several large studies have found that actionable PGx variants are common in the general patient population. Additionally, the FDA has approved PGx tests and many more have been developed as laboratory developed tests.

Yet, despite availability of PGx tests and some evidence for their utility, it remains largely unclear under what circumstances PGx tests should be ordered and how best to address the logistic challenges of incorporating PGx test results into medical records, workflow (preemptive testing versus at the time of drug ordering), and clinical decision making.

A Scan of Commercially Available PGx Testing

In what is described as the first published horizon scan of commercially available PGx tests, researchers from Duke University assessed the range and types of PGx tests offered by laboratories nationally. The results, published in the May issue of *Health Affairs*, show that available PGx tests vary in type and makeup, which presents a challenge for providers, health system, and insurers, alike.

In order to identify the numbers and types of PGx tests offered by clinical laboratories in the United States from September 2017 to January 2018 the researchers used data from the National Institutes of Health (NIH) Genetic Testing Registry, the McKesson Diagnostics Exchange, the Association for Molecular Pathology's Test Directory, published literature, and internet searches. They excluded laboratories that offered testing for research purposes only or those offering only companion diagnostics for targeted therapies.

Particular interest was paid to tests that include the 13 genes (CYP2C9, CYP2C19, CYP2D6, CYP3A5, CYP4F2, DPYD, G6PD, HLA-B, IFNL3, SLCO1B1, TPMT, UGT1A1, and VKORC1) included in the Clinical Pharmacogenetics Implementation Consortium's (CPIC's) guidelines.

Acknowledging that they likely underestimated the number of laboratories offering PGx testing, the researchers identified 111 clinical labs offering PGx testing, but were only able to confirm the PGx offerings of 76. Of the confirmed laboratories, 31 offered only tests for single genes; 30 offered only tests for multiple genes; and 15 offered both.

"With the exception of the gene pairs CYP2C9/VKORC1 for warfarin and CYP2C9/HLA-B for phenytoin (brand name Dilantin), all of the CPIC guidelines focus on a single gene-drug or gene-drug class interaction."

— Susanne Haga

Among the 46 laboratories that offered single-gene PGx testing, a total of 219 tests were available for 13 genes ranked as having high evidence (grade A) by CPIC. However, five genes (CYP2C9, CYP2C19, CYP2D6, CYP3A5, and VKORC1) accounted for nearly three-quarters of these tests. None of the laboratories offered individual PGx tests for all 13 genes, but they offered a mean of five tests each.

In total, 45 laboratories offered 114 multigene panel tests covering 295 genes. Specialty labs, which offered only PGx testing, were the most common providers of multigene PGx panels (nearly 30 percent), followed by genetic testing labs that offered a range of genetic tests (nearly 25 percent). Laboratories offered a mean of three multigene PGx panels (range one to nine panel tests). Panel sizes ranged from 2 to 231 genes, with a mean of 14 genes covered. Most of the panel tests included at least some of the thirteen genes ranked "A" by CPIC. Again, the most commonly included gene was CYP2D6.

Panel testing can theoretically reduce the testing burden and cost on physicians, laboratories, patients, and payers, and may hold value in the realm of preemptive testing, multigene panel tests may present challenges for test comparison, test selection, insurance coverage, and patient counseling.

"With the exception of the gene pairs CYP2C9/VKORC1 for warfarin and CYP2C9/HLA-B for phenytoin (brand name Dilantin), all of the CPIC guidelines focus on a single gene-drug or gene-drug class interaction," writes coauthor Susanne Haga, from Duke University in Durham, N.C. "The combined effect of variations in multiple genes relevant to a given medication remains largely unknown, though some test developers have suggested that combinatorial PGx testing … may provide a more comprehensive prediction of drug response by using proprietary algorithms to predict drug safety and may reduce medication costs."

A Case Study for PGx Policy Recommendations

With uncertainty about the clinical utility of PGx testing, particularly for multigene PGx panels, the experiences of health systems that have been early PGx adopters can inform other provider groups.

As an integrated system with a common electronic health record that includes both laboratory test results and pharmacy records, the Veterans Health Administration (VHA) is uniquely positioned to incorporate and benefit from PGx testing in routine patient care. The VHA's Clinical Pharmacogenetics Subcommittee is charged with making recommendations for standardizing PGx testing across VHA care facilities. The subcommittee recently published a case study in the June issue of *Genetics in Medicine* elucidating how the process for reviewing the scientific evidence for and making policy recommendations about routine PGx use.

The subcommittee used an "ACCE model" that evaluates each PGx test by its:

- Analytic validity - ability to accurately identify the genotype of interest
- Clinical validity - the likelihood that the test result (genotype) provides information about therapeutic efficacy or toxicity
- Clinical utility - the likelihood that PGx information will lead to a change in clinical management that improves health outcomes
- Ethical, legal, and social implications

After developing these consensus definitions, the subcommittee identified 30 relevant drug-gene pairs (from the NIH's PharmGKB and CPIC recommendations) that would be potentially applicable in the VHA setting. Companion diagnostics were excluded. Reviewers used databases of clinical and research PGx groups from the government and private sector in order to complete a review template that included the indications for drug use, mechanism of action, pharmacokinetics, and PGx of the medication for each drug-gene pair. The subcommittee discussed each drug-gene pair and classified each test as strongly recommended (13 percent), recommended (40 percent), or not routinely recommended (47 percent) before drug initiation.

Examples of VHA Drug-Gene Pair Recommendations

- **Strongly recommended:** If the phenotype was a severe adverse drug effect that could be avoided with alternative therapy (e.g., HLA-B*15:02 for carbamazepine-associated Stevens-Johnston syndrome and G6PD for rasburicase-associated hemolytic anemia)
- **Recommended:** Could inform either the risk of an adverse drug effect or drug efficacy (e.g., CYP2D6 for codeine toxicity)
- **Not routinely recommended:** Informs drug efficacy but lacked studies demonstrating improved patient outcomes (e.g., CYP2C19 for clopidogrel dosing)

The subcommittee acknowledged consideration of other factors aside from the recommendations, such as feasibility, cost, and patient and provider acceptance will inform ultimate national VHA policy for PGx testing.

"The subcommittee's recommendations do not contradict the work of PharmGKB or CPIC but, rather, highlight the need for demonstrated improvements in patient outcomes before large health care systems might broadly implement PGx testing outside of a research context," writes lead author Jason Vassy, M.D., from the VA Boston Healthcare System in Massachusetts, on behalf of the VHA Clinical Pharmacogenetics Subcommittee. "No one approach to evidence review and policymaking will apply to all health care contexts. ... Continual evidence review and rigorous outcomes research will help promote the translation of PGx discovery to health care."

Application of PGx to Prescribing for Depression

While PGx initially focused heavily on warfarin testing to prevent bleeding for those initiating anticoagulation therapy, there is increasing

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>
> — Bryan Dechairo, Ph.D.

interest on the application of PGx to aid dosing of antidepressants and other psychiatric agents. FDA's boxlist of warnings includes 27 medications commonly used in psychiatric practice to treat mood and anxiety disorders. Two laboratories offering commercially available PGx panels for psychiatric dosing recently presented the results of large clinical trials.

Patients with depression whose medication selection was guided by the GeneSight Psychotropic PGx test saw significant improvements in remission, response and symptoms when treated by both primary care physicians and psychiatrists, according to Myriad Genetics (Salt Lake City). The company recently presented these results from its Individualized Medicine: Pharmacogenetics Assessment and Clinical Treatment (IMPACT) study at the American Society of Clinical Psychopharmacology's annual meeting (May 29-June 1; Miami, Fla.).

The IMPACT study evaluated the clinical utility of the GeneSight test in selecting medications for 2,025 patients with moderate to severe major depressive disorder. All patients were assessed using the Beck Depression Inventory at baseline (Day 0) and at follow-up (Week 8-12).

The researchers found that when clinicians used the GeneSight test results to guide medication selection, patients saw a significant 28 percent mean reduction in symptoms. Additionally, 26 percent of patients responded to treatment and 17 percent achieved remission. Perhaps most importantly, there were significantly greater improvements in outcomes for patients treated by primary care providers versus psychiatrists. (This difference may be explained by the fact that psychiatrists may care for complex cases.)

"Most patients with depression are treated by primary care providers who select antidepressant medications using a trial and error approach," said Bryan Dechairo, Ph.D., executive vice president of clinical development at Myriad Genetics, in a statement. "The IMPACT study demonstrated the clinical value of the GeneSight test to guide medication selection in the primary care setting."

The benefits of PGx in the psychiatric care stetting may also include economic savings resulting from decreased utilization of health care, according to a study (funded by Genomind) published May 7 in the journal Depression and Anxiety.

The researchers used Aetna claims data to identify patients with non-newly diagnosed mood disorders who had two or more failed treatments. The intervention group (n=817; assay-guided treatment group) had received the commercially available Genecept assay (Genomind Inc.; King of Prussia, Penn.) from January 2012 through December 2015. The usual treatment group (n=2,745 controls) were propensity matched based on diagnosis, duration of illness, comorbidities, number of prior treatment failures, age, gender, and socioeconomic status.

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The researchers found that those who had assay-guided treatment experienced 40 percent fewer emergency room visits and 58 percent fewer inpatient hospitalizations than individuals in the control group during the six-month follow-up period. The two groups did not differ significantly in number of psychotropic medications prescribed or mood disorder-related hospitalizations.

The decrease in utilization of health care services translated to a significant reduction in overall health care costs. Based on claims data, the researchers estimated that the subsequent six-month cost of care was $1,948 lower per individual in the assay-guided treatment group versus the control group, although these costs did not include cost of the PGx test, estimated to be $750 for contracted health plans.

Takeaway: PGx testing remains in an early stage of clinical adoption. Additional outcomes research is necessary to promote the translation of PGx discovery into patient care.

Whole-Genome Sequencing Can Improve Blood Transfusion Matches, *from page 1*

"Blood transfusion complications are common in patients needing chronic transfusion, but with current technology it is not cost effective to do blood typing for all antigens," said lead study author William Lane, M.D., Ph.D., director of clinical laboratory informatics at Brigham and Women's Hospital, in a statement. "But the algorithm we have developed can be applied to type everyone for all relevant blood groups at a low cost once sequencing is obtained."

There are more than 11 million units of blood transfused annually in the United States, but today, most pre-transfusion compatibility testing for includes only ABO and Rh matching using serological methods. While extended antigen matching can improve transfusion safety, it is not currently the standard of practice, largely because serological methods are labor-intensive, costly, and reagent antibodies are not available for many clinically important blood-group antigens, the authors say. Even DNA array methods that use single nucleotide polymorphisms are unable to target all blood groups.

The researchers created a database of RBC and platelet antigen alleles based on published articles and developed an automated antigen-typing algorithm (bloodTyper) based on WGS. Development and initial validation of the algorithm was based on secondary analysis of 110 participants randomized to the WGS group of the MedSeq Project with sequencing (30 x depth) performed on the Illumina HiSeq 2000 platform (Illumina, San Diego, CA, USA). Performance of the algorithm was compared to conventional serology and SNP methods for typing of 38 RBC antigens in 12 blood-group systems and 22 human platelet antigens. bloodTyper was then further validated with WGS data from 200 INTERVAL trial participants (15 × depth) with serological comparisons.

The researchers found that the initial WGS typing algorithm was 99.5 percent concordant across the first 20 MedSeq genomes. Resolving the discordances led to development of an improved algorithm that was 99.8 percent concordant for the remaining 90 MedSeq genomes. Additional iteration led to the final algorithm, which was 99.2 percent concordant across the 200 INTERVAL genomes or 99.9 percent after adjusting for the lower depth of coverage.

"Our automated analytical software algorithm could be transformative in the implementation of population-level RBC and platelet antigen typing," write Lane and colleagues. "The ability to test large populations of donors and recipients for clinically important antigens that do not have serological reagents could greatly reduce transfusion-related morbidity and mortality. As whole-genome sequencing becomes more common in clinical practice, secondary analysis of existing data could allow inexpensive, comprehensive blood-group typing to become part of donor and patient medical records.

Takeaway: This novel WGS-based approach can improve the standard of practice for transfusion medicine, potentially improving blood matches and patient outcomes.

Early Lactate Tests Impactful, But Often Not Performed With Sepsis

Early lactate measurements appear to improve results for patients with sepsis, but initial and repeat serum lactate levels are frequently not drawn in the recommended six-hour window, according to a study published online May 24 in the journal *CHEST*. The authors say that delays in lactate measurements for patients with initial abnormal values are associated with progressive increases in mortality.

In 2015 the Centers for Medicare & Medicaid Services introduced the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) to improve timely diagnosis and management of sepsis. The bundle requires providers to measure serum lactate, obtain blood cultures, and initiate antibiotics within a specified time window (An initial serum lactate level must be drawn between six hours before and three hours after severe sepsis presentation, followed by a repeat measurement within six hours of presentation if the initial value is elevated.) But, inclusion of serum lactate measurement proved to be controversial among sepsis experts.

Researchers from the University of Chicago sought to understand the impact of the bundle of recommendations on patients, so they retrospectively applied apply the SEP-1 definitions (two systemic inflammatory response syndrome criteria, display at least one new organ dysfunction, and documentation of suspicion of infection) to all adults admitted to the University of Chicago (n=149,6000) from November 2008 to January 2016. Time to lactate draw, antibiotic and IV fluid administration, and in-hospital mortality were evaluated.

Based on the 5,762 patients meeting all three SEP-1 criteria, the researchers found that overall, 60 percent of patients had an initial lactate drawn with-

> *"Systematic early lactate measurement for all patients with sepsis will lead to a significant increase in lactate draws that may prompt more rapid physician intervention for patients with abnormal initial values."*
>
> — Xuan Han, M.D.

in the SEP-1-specified time, but there was variance by patient location. The mandated window was met only 32 percent of the time on the ward versus 55 percent of the time in the ICU and 79 percent of the time in the emergency department.

"Sepsis bundles have often focused on emergency department patients, but our study demonstrates that a large number of patients become newly septic on the wards and have higher mortality than those who initially meet criteria in the emergency department. This is an important population of patients in which to effectively and quickly identify and treat sepsis.

Delayed lactates (lactate samples drawn from three to 24 hours after the time of suspicion of infection) occurred for 14 percent of the patients meeting severe sepsis criteria. More than one-quarter of patients with sepsis (26 percent) did not have a lactate drawn within 24 hours of suspicion of infection.

Patients with delayed lactate measurements demonstrated the highest in-hospital mortality (29 percent) and had increased time to antibiotic administration. Patients with abnormal initial lactates (> 2.0 mmol/L) showed a significant increase in the odds of death for each hour of delay in lactate measurement. Lastly, length of stay was longest for patients who never had lactates drawn (median, 18 days), followed by those with delayed lactates (median, 15 days), versus 11 days for patients who had a lactate sample drawn in the SEP-1 window.

"Systematic early lactate measurement for all patients with sepsis will lead to a significant increase in lactate draws that may prompt more rapid physician intervention for patients with abnormal initial values," write the authors led by Xuan Han, M.D.

Takeaway: This study adds evidence that systematic early lactate measurements in suspected patients with sepsis can positively affect outcomes, including time to intervention, mortality, and length of stay.

Men Undergo Hereditary Cancer Testing Less Frequently Than Women

Unaffected men undergo genetic cancer testing at half the rate of unaffected women, according to a research letter published April 26 in *JAMA Oncology*. This disparity in testing is attributable to a 10-to-1 gender difference in testing for hereditary breast and ovarian cancer, the authors say.

Up to 10 percent of cancers are hereditary in nature, including BRCA1/2 that are responsible for hereditary breast and ovarian cancer. While genetic testing in women predominates headlines, carrier rates are actually equivalent between men and women.

The researchers used data from the 2015 US National Health Interview Survey in order to national distribution of genetic testing for hereditary cancer risk. For those reporting they underwent genetic testing, sociodemograph-

ic differences were evident, including a significantly lower proportion of Hispanics, uninsured patients, noncitizens, and those with less education. Overall, almost three times as many women received testing than men (73 percent versus 27 percent).

Three-quarters of reported genetic testing was for breast/ovarian cancer, one-quarter for colorectal cancer, and 22 percent for other cancers. There were no gender disparities for colorectal or other cancer testing, but for testing for breast/ovarian cancer, men underwent at one-tenth the rate of women.

"Previous theories for underutilization of hereditary breast and ovarian cancer testing in men include lack of patient and clinician awareness on the importance of hereditary breast and ovarian cancer mutation status—despite the risks of male breast, pancreatic, melanoma, and aggressive prostate cancers," write the authors led by Kimberly Childers, a genetic counselor at Providence Health & Services Southern California, Los Angeles. "Large national efforts, including educational campaigns targeting male HBOC testing, must address this disparity to enable uniform opportunities for cancer prevention, early detection, and treatment for all at-risk individuals and their family members."

Takeaway: Some groups remain underrepresented in receipt of cancer genetic testing, including men for hereditary breast and ovarian cancer testing.

Single-Sample Confirmatory Test Okay for Diabetes Diagnosis

A single blood sample can be used to test for both fasting glucose and hemoglobin A1c (HbA1c) levels in order to identify undiagnosed diabetes in the population, according to a study published in the *Annals of Internal Medicine*. This confirmatory definition, the authors say, has high positive predictive value for future risk for diagnosed diabetes and is associated with risk for major clinical outcomes.

Current clinical definitions of diabetes often require repeated testing to confirm elevated levels of glucose or HbA1c in order to reduce the possibility of a false-positive diagnosis.

"Using a repeated test on a new sample from a subsequent visit to confirm diabetes can be logistically cumbersome, inconvenient, and expensive and can delay patient care," writes K.M. Venkat Narayan, MD, from Emory University in Atlanta in an editorial accompanying the study. "Whether two tests from the same blood sample can be used for both screening and confirmation is an intriguing question with practical relevance."

In the present study researchers analyzed 25-year data from 12,268 participants of the Atherosclerosis Risk in Communities) study without diagnosed diabetes at baseline. Confirmed, undiagnosed diabetes was defined as elevated levels of fasting glucose (≥7.0 mmol/L and HbA1c (≥6.5%) from a single blood sample. Unconfirmed undiagnosed diabetes was defined as no diagnosis and only one elevated measured.

"This study provides construct validity for a confirmatory definition of undiagnosed diabetes that is based on a combination of HbA1c and fasting glucose measured in a single blood sample."

— Elizabeth Selvin, Ph.D.

The researchers found that at baseline (1990 to 1992), 978 participants had elevated levels of fasting glucose or HbA1c. Among these, 39 percent had both measures elevated (confirmed undiagnosed diabetes), while 61 percent had only one elevated measure (unconfirmed undiagnosed diabetes).

For identifying diabetes cases diagnosed during the first five years of follow-up, the confirmatory definition had moderate sensitivity (54.9 percent) but high specificity (98.1 percent). Specificity increased to 99.6 percent by 15 years, with a 15-year positive predictive value of 88.7 percent versus 71.1 percent for unconfirmed cases.

"This study provides construct validity for a confirmatory definition of undiagnosed diabetes that is based on a combination of HbA1c and fasting glucose measured in a single blood sample," write the authors led by Elizabeth Selvin, Ph.D. from Johns Hopkins University in Baltimore, Md. "Our data suggest high general concordance between fasting glucose and HbA1c levels; therefore, attention should be paid to any sizeable discordance between them because this may indicate a sample processing problem or a coexisting medical condition that may be interfering with either test."

Takeaway: Simplifying methods to screen for and confirm diabetes can facilitate clinical care of the individual and can benefit population-level efforts to identify diabetes at an earlier stage.