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New Trends, Applications, and IVD Industry Analysis

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New Studies Question Utility of Gene Expression Testing for Cancers With Unknown Primary Site, Low-Risk Breast Cancer

Gene expression profiling has been making inroads into clinical cancer care, with application in cancer classification, most notably with breast cancer. Two recent studies are calling into question the clinical utility and the cost-effectiveness of such tests.

Cancers of Unknown Origin

For patients with cancer of unknown primary site (CUP), use of microarray profiling to guide site-specific cancer treatment does not result in a significant improvement in survival compared to empirical treatment, according to a phase II Japanese study published Jan. 17

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Genetic Risk of Prostate Cancer Underestimated; Testing Guidelines Miss Men With Elevated Prostate Cancer Risk

Neither guideline eligibility nor Gleason scores are reliable for predicting prostate cancer risk due to pathogenic germline variants, according to a study published Feb. 7 in JAMA Oncology. The authors say that expanding genetic testing guidelines will improve medical management of prostate cancer patients and their families.

"We propose that genetic testing guidelines should be simplified and expanded to include genetic testing of all men diagnosed with prostate cancer similar to guidelines for pancreatic and colorectal cancer," say study coauthors led by Piper Nicolosi, Ph.D., from Invitae Corp. (San Francisco, Calif.), which also conducted the testing. "Simplification of testing guidelines would facilitate informed decision making for patients and their family members and provide the foundation for cascade testing of at-risk relatives before they develop cancer, initiating both surveillance and risk-reduction options."

Inherited risk for prostate cancer is associated with aggressive disease

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New Studies Question Utility of Gene Expression Testing for Cancers, *from page 1*

in the *Journal of Clinical Oncology*.

"With the increasing number of effective molecularly targeted therapies available as well as the recent success of immunotherapies for several types of cancer, the gap in treatment advances between CUP and known primary cancer is widening," write the authors led by Hidetoshi Hayashi, MD, PhD, from Kindai University in Japan.

Gene expression profiling that has the potential to predict the origin of tumor tissue for patients with metastatic disease of unknown origin, based on the basis of site-specific expression profiles.

In this clinical trial, comprehensive gene expression profiling was performed on frozen biopsy tissue using microarray analysis. An established algorithm was applied to results to predict tumor origin. Tissue of origin was predicted for all 130 patients across 16 different anatomical sites—pancreatic and gastric cancer and malignant lymphoma were the three most common predicted primary sites, accounting for approximately 60 percent of all patients. From consent to results took 3 weeks. Based on these results, patients were randomized (1:1) to receive either site-specific therapy or empirical chemotherapy based on test results between October 2008 and February 2015.

The researchers found that the 1-year survival rate was similar between the site-specific and empirical treatment groups, as were median overall and progression-free survival. No subgroup of patients showed a significant benefit in terms of overall survival from site-specific treatment.

"Despite an accuracy rate of 78.6 percent for site prediction in silico, our results suggest that comprehensive genome-wide profiling of gene expression by microarray analysis might not yet be suitable for clinical application inpatients with CUP," the authors conclude. "However, the observation that patients predicted to have more-responsive tumor types had a better OS and PFS than those with less-responsive tumor types suggests that pre-diction of original tumor site has prognostic value."

Low-Risk Breast Cancer

OncotypeDx (ODX; Genomic Health; Redwood City, Calif.) is the most commonly used tumor profiling test and is included in practice guidelines worldwide. However, a new study, published in the January issue of the Journal of the National Comprehensive Cancer Network, is questioning the tests' cost-effectiveness in women with a low clinical risk of breast cancer recurrence.

Unlike previous analysis, this study examined cost-effectiveness by a patients' risk category, as determined by clinical and pathologic features. This analysis did confirm the tests' cost effectiveness in intermediate- and high-risk estrogen receptor (ER)–positive, HER2-negative, lymph node–negative breast cancer.

ODX, a 21-gene assay, is widely used in clinical practice to accurately identify

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patients who would benefit from chemotherapy. Using gene-expression profiling, the test provides a recurrence score (RS) between 0 and 100, with scores categorized as low (RS < 18), intermediate (18 ≤ RS ≤ 30), or high (RS ≥ 31) risk.

The authors note that the previous analyses that concluded ODX is cost-effective for all women with ER-positive, node-negative breast cancer had "important methodologic limitations" in that they combined all patients into one group, regardless of clinical and pathologic features.

> *"Such an approach, ignoring tumor characteristics when evaluating ODX, is not consistent with actual clinical practice because it assumes that all patients would be treated without consideration of their clinical characteristics."*
>
> — Shi-Yi Wang, M.D., Ph.D.

"Such an approach, ignoring tumor characteristics when evaluating ODX, is not consistent with actual clinical practice because it assumes that all patients would be treated without consideration of their clinical characteristics," write the authors led by Shi-Yi Wang, M.D., Ph.D., from Yale University in New Haven, Conn.

The new analyses used data from the Connecticut Tumor Registry to identify 4,281 women diagnosed with ER-positive, HER2-negative, node-negative breast cancer between 2011 and 2013. Just over half of these women (54.6 percent) received ODX testing. The researchers classified the 2,245 patients into 3 clinical risk groups according to the PREDICT model, a risk calculator developed by the National Health Service in the United Kingdom.

The researchers found that the PREDICT risk calculator categorized the sample as 82.5 percent low-, 11.9 percent intermediate-, and 5.6 percent high-risk. When the three groups were combined, ODX had an incremental cost-effectiveness ratio (ICER) of $62,200 per QALY for patients aged 60 years. However, ICERs, differed substantially across clinical risk groups, ranging from $124,600 per quality-adjusted life years (QALY) in the low-risk group, to $28,700 per QALY in the intermediate-risk group, and $15,700 per QALY in the high-risk group.

There was also substantial variability in the cost-effectiveness of ODX when considering variation in life expectancy and age-based utility weights. ICERs ranged from $77,100 per QALY for patients aged 45 years to $344,600 per QALY for patients aged 75 years in the PREDICT low-risk group. In the intermediate- and high-risk groups QALYs remained lower than the $100,000 threshold for women aged 45 to 75 years.

"Given that most women in our population-based sample were classified as low risk, our study suggests that clinicopathologic information needs to be incorporated in ODX testing decision-making," writes Wang and colleagues.

Despite the cost concerns raised, some experts are wary to change clinical practice immediately.

"I applaud any efforts to reduce unnecessary testing and chemotherapy in patients where there is no benefit," said Lori Goldstein, M.D., a member of

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the National Comprehensive Cancer Network (NCCN) Guidelines Panel for Breast Cancer. "While the present analysis raises some thoughtful questions, until future prospective randomized trials are able to further help confirm subsets of patients with no clear benefit from additional chemotherapy, the NCCN recommendations remain appropriate. The current costs associated with the ODX test seem justifiable based on patient benefit."

Takeaway: While the long-term utility of gene expression profiling is not in question, these studies raise some questions about optimizing testing to most cost-effectively inform patient care.

Donor-Derived, Cell-Free DNA May Predict Lung Transplant Rejection

Elevated donor-derived, cell-free DNA (ddcfDNA) in the 3 months post-lung transplant can identify clinically silent allograft injury and predict progression to chronic rejection, according to a proof-of-concept study published Jan. 26 in EBioMedicine. Early identification of patients at risk for developing allograft failure could provide a window of opportunity to address immunologic mechanisms that left unaddressed could progress to transplant rejection.

"This is the first report of a method to detect and quantify clinically silent, but likely pathological, events preceding allograft failure," write the authors led by Sean Agbor-Enoh, M.D., Ph.D., from the National Heart, Lung and Blood Institute in Bethesda, Md. "These underlying events, uncovered through our analysis of [levels of] ddcfDNA, may help to explain the unacceptably high rate of chronic lung allograft dysfunction that remains the Achilles heel of lung transplantation."

It is estimated that half of all lung transplants fail within 5 years due to chronic rejection, a rate higher than for other solid organ transplants. This failure, called chronic lung allograft dysfunction (CLAD), includes bronchiolitis obliterans syndrome (BOS), which is the most common subtype. Despite these high rates of transplantation failure, there is no current predictor for which patients are at risk for developing BOS and chronic lung transplant rejection. Yet, prior research shows that fragments of ddcfDNA result from cell injury and cell death and are detectable in the blood of transplant recipients.

The researchers prospectively monitored 106 subjects who underwent lung transplantation at multiple institutions for allograft failure. A total of 1,145 plasma samples (9.7 samples per patient) were collected serially in the first three months following transplantation and assayed for percent ddcfDNA using shotgun sequencing. Average levels of ddcfDNA (avddDNA) over the three months were calculated for each patient.

The researchers found that all three groups for average levels of ddcfDNA (low, middle, and upper tertiles) showed high immediate post-transplant ddcfDNA levels with variable levels of ddcfDNA decay. Median values for avddDNA were highly variable (range 0.1 percent to 9.9 percent)— 3.6 percent for the upper, 1.6 percent for the middle, and 0.7 percent for the low tertile.

Overall, a 1 percent increase in avddDNA increased the risk of allograft failure 1.4-fold, the risk of CLAD or death by 1.5-fold, and all-cause death by 1.5-fold. However, those in the upper tertile had a 6.6-fold higher risk of developing allograft failure, a 7.8-fold higher risk of CLAD or death, and a 3.9-fold higher risk of all-cause mortality compared to the subjects in the low avddDNA tertile.

"Only one-third of these elevated %ddcfDNA episodes were associated with acute rejection or clinical infection," explain the authors. "The remainder were not coincident to any signs detectable by histopathology, spirometry, clinical examination, or by any other clinical tests. These episodes of clinically silent elevations in %ddcfDNA could represent early detection of injury that progresses to pathologically overt changes."

While experts are optimistic that with further validation ddcfDNA may be a clinically relevant, noninvasive marker of early allograft injury, particularly for lung transplant recipients, there is some concern that options to intervene remain limited.

"While this assay provides an early detection for BOS, there currently are no therapeutic modalities to prevent or cure chronic lung rejection once it is established," writes Sandhya Bansal, Ph.D., the coauthor of a related commentary published Feb. 5. "However, this method for early detection of BOS does allow researchers to evaluate changes in immune modulatory molecules and T regulatory cells that may prove to be important in developing novel treatment strategies."

Takeaway: Elevated levels of ddcfDNA in the early months post-lung transplant may be able to predict long-term outcomes, including progression to chronic rejection, even in the absence of traditionally detectable clinical signs of rejection.

Calprotectin May Predict Arthritis Relapse

Baseline calprotectin serum levels independently predicted disease relapse in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) taking tumor necrosis factor inhibitors (TNFi) therapy, according to a study published online Dec. 13, 2018 in *Arthritis Research & Therapy*. Predicting relapses could improve care and avoid related costs, the authors say.

Calprotectin, a proinflammatory factor, is a known biomarker of disease activity and predicts relapse in juvenile idiopathic arthritis. The present study analyzed the accuracy of serum calprotectin levels and drug trough serum levels (TSL) to detect subclinical disease activity and predict relapse in RA and PsA patients. Enrolled patients were in remission or had low disease activity while receiving TNFi (March 2013 to September 2014). While 103 patients (47 RA, 56 PsA) enrolled at a single center, only 95 completed one year of follow-up.

Calprotectin serum levels, TNFi trough serum levels, and antidrug antibodies were evaluated at baseline and during disease relapse using an enzyme-linked immunosorbent assay test kit. Additionally, serum samples were collected at 4, 8, and 12 months of follow-up to assess longitudinal changes in drug trough serum levels.

> *"Calprotectin may be used to stratify disease activity more accurately in patients with low disease activity, guiding therapeutic decisions towards safer and more cost-effective strategies,"*
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> — José Inciarte-Mundo, University of Barcelona

Over the year of follow-up, 12 patients experienced a relapse. While time-to-remission/low disease activity, calprotectin levels and TNFi TSL were significantly associated with disease relapse, only baseline calprotectin levels independently predicted disease relapse. Calprotectin fully predicted relapse (area under the curve, 1.00). An optimal calprotectin level of 3.7 µg/mL predicted relapse. This calprotectin cut-off level had a sensitivity of 100 percent and a specificity of 98.8 percent for the diagnosis of a relapse with a positive likelihood ratio of 83 and a negative likelihood ratio of 0.

Serum samples were analyzed during relapse and a significant increase in calprotectin levels was seen in 10 of 12 patients, while TNFi trough serum levels decreased in all relapsers compared with baseline values.

"Calprotectin may be used to stratify disease activity more accurately in patients with low disease activity, guiding therapeutic decisions towards safer and more cost-effective strategies," write the authors led by José Inciarte-Mundo, from University of Barcelona in Spain.

Takeaway: Baseline serum levels of calprotectin may identify residual, subclinical inflammatory activity in patients with low RA or PsA disease activity and can serve as a strong predictor of disease relapse.

INSIDE THE DIAGNOSTICS INDUSTRY

Exome Sequencing Improves Diagnosis of Fetal Structural Anomalies

Prenatal diagnostics have evolved from conventional cytogenetic analysis to increasingly chromosomal microarray analysis, within the last 10 years. While whole-exome sequencing (WES) has shown utility in identifying genetic causes of developmental disorders in children, up until now there has been limited evidence evaluating the usefulness of WES for the diagnosis and clinical management of ultrasound-detected fetal anomalies.

Two recent studies, both published Jan. 31 in *The Lancet*, show that the addition of whole-exome sequencing (WES) improves genetic diagnosis of fetal structural anomalies, which, in turn, can facilitate better determination of fetal prognosis and risk of recurrence in future pregnancies.

It is estimated that roughly 3 percent of pregnancies will have a fetal structural anomaly detectible on ultrasound, which can range from a single minor defect to severe, fatal multisystem anomalies. Currently, when fetal structural anomalies are detected, a routine workup would include testing for aneuploidy and copy number variations (CNVs). The two Lancet studies, which both included fetuses pre-screened for pathogenic chromosomal abnormalities or CNVs but with a wide range of structural anomalies, consistently demonstrated clinically significant genetic variants in 8.5 percent to 10.3 percent of fetuses and that the majority of these diagnostic variants in both studies were from de-novo mutations.

"We suggest that these studies serve as the introduction of WES into prenatal testing and document a compelling justification for its adoption," write Michael Talkowski and Heidi Rehm, both from Massachusetts General Hospital (Boston) in an accompanying commentary. "The technology is mature, the data are reproducible, and the processes are established in many clinical laboratories."

Technically WES creates "voids," experts say, in its inability to screen for CNVs, balanced chromosomal abnormalities, and complex structural variation, meaning that a combination of WES and molecular cytogenetic methods represents the most "comprehensive" viable approach for routine prenatal genetic testing.

The U.K. PAGE Study

The Prenatal Assessment of Genomes and Exomes (PAGE) study recruited women with fetuses with structural anomalies between Oct. 22, 2014, and June 29, 2017, from 34 fetal medicine units in England and Scotland. Samples were taken from fetuses without aneuploidy and large CNVs and their parents (596 fetus–parent trios, 14 fetus–parent dyads). Sequencing results were interpreted using a targeted virtual gene panel consisting of 1,628 genes implicated in developmental disorders (n = 1,511) and other prenatal findings (n = 117). Genetic results were returned post-pregnancy.

Following bioinformatic filtering and prioritization according to allele frequency and

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Exome Sequencing Improves Diagnosis of Fetal Structural Anomalies, *from page 7*

effect on protein and inheritance pattern, the researchers identified 321 genetic diagnostic genetic variants, representing 255 potential diagnoses (0.42 potential diagnoses per fetus). A multidisciplinary clinical panel reviewed variants.

Overall, a clinically significant genetic variant was identified in 8.5 percent of fetuses, with an additional 3.9 percent of fetuses having variants of possible clinical significance. The proportion of fetuses with diagnostic genetic variants varied by phenotype: 3.2 percent in fetuses with increased nuchal translucency, 11.1 percent in those with cardiac anomalies, and 15.4 percent in those with skeletal or multisystem fetal structural anomalies. Just over one-third of diagnostic genetic variants had a high recurrence risk.

The authors, led by Jenny Lord, Ph.D., from the Wellcome Sanger Institute in the United Kingdom, acknowledged that although WES increases the frequency of identification of genetic causes of structural anomalies in fetuses more than cytogenetics or chromosomal microarray alone, the overall frequency of diagnostic genetic may have been lower than expected. Based on their experience, the researchers advise the use of

- Fetal-parental trio analysis rather than fetus-only WES to speed identification of de-novo variants in monoallelic developmental disorder genes
- Selected subgroups (e.g., those with multiple congenital anomalies) or after genetic review
- Curating the developmental disorders gene to phenotype list to remove genes not associated with fetal structural anomalies and using smaller, phenotype-specific virtual gene panels, to reduce the number of variants of unknown significance that are irrelevant to the fetal structural anomalies.

A U.S.-Based Study

In the second study, researchers from Columbia University in New York screened consecutive fetuses with structural anomalies (April 2015 to April 2017) and performed WES on 234 fetus–parent trios. WES was offered to all patients, regardless of the anomaly, but a substantial portion of parents (24 percent) declined testing or did not consent to WES.

This study used a tiered interpretation approach incorporated bioinformatic signatures. This allows variants in genes not yet linked to disease to be considered if they had similar properties to variants that occur at higher frequency in developmental disorders relative to their occurrence in the general population. While this approach increases sensitivity it also increases interpretation workload. The researchers identified 1,182 qualifying genotypes that warranted consideration (a mean of 4.8 qualifying genotypes per fetus, which is ten times the number identified in the PAGE study). After review by the multidisciplinary panel, this interpretation approach yielded molecular diagnoses in 2 percent of the 1,182 variants considered.

Overall, a diagnostic genetic variant was identified in 10.3 percent of fetuses. Further, mutations suggestive of pathogenicity, but with insufficient evidence to be considered diagnostic, were identified in 20 percent of fetuses.

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Similar to the PAGE study, the proportions of fetuses with a diagnostic variant varied by phenotype: 5 percent with cardiac, 16 percent of fetuses with renal, 22 percent with central nervous system, and 24 percent of fetuses with lymphatic/effusion or skeletal anomalies.

A genetic diagnosis was achieved three times more often in fetuses with several anomalies versus those with one anomaly (19 percent versus 6 percent). In fetuses with three or more anomalies, a diagnostic genetic variant was identified in more than 30 percent of cases.

The authors, led by Slavé Petrovski, Ph.D., from Columbia University in New York, recommend that

- Interpretation of prenatal sequencing involves collaboration of a multidisciplinary team, including clinical and molecular geneticists, genetic counselors, and fetal imaging specialists
- Workflow must be optimized to minimize turnaround time so that results are returned in a timeframe conducive to decision-making in the "time-compressed" prenatal setting.

Takeaway: WES can improve upon the diagnostic capabilities of karyotyping and microarray analysis to find a diagnostic variant responsible for ultrasound-detected structural anomalies in fetuses. While WES is both clinically useful and feasible, some important questions remain regarding fetal selection, the number and type of genes to be interrogated, how to improve turnaround time to deliver results in an actionable timeframe, and which results to return and when.

Genetic Risk of Prostate Cancer Underestimated, *from page 1*

and poorer outcomes and has implications for staging, screening, guiding treatment, genetic counseling, and cascade testing of family members. However, genetic testing guidelines are complex and inconsistent between organizations.

The present study evaluated the presence of pathologic variants in 3,607 men with a personal history of prostate cancer (mean age at diagnosis, 60 years) who underwent referral-based, germline testing between 2013 and 2018. Testing evaluated 14 genes on the Invitae curated prostate cancer panel (ATM, BRCA1, BRCA2, CHEK2, EPCAM, HOXB13, MLH1, MSH2, MSH6, NBN, PMS2, TP53, RAD51D, and PALB2) for 2,250 orders. For the remaining 38 percent of orders, analysis of other genes was ordered from larger hereditary cancer panels or through customized requests. The price of a panel was the same regardless of the genes tested, so variation was dependent on clinician preference.

The researchers found that 17.2 percent of men had a pathogenic germline variant, with the top 10 genes as a percentage of men tested being: BRCA2, (4.74 percent), CHEK2 (2.88 percent), ATM (2.03 percent), MUTYH (2.37 percent), APC (1.28 percent), BRCA1 (1.25 percent), HOXB13 (1.12 percent), MSH2 (0.69 percent), TP53 (0.66 percent), and PALB2 (0.56 percent). Positive variants in mismatch repair genes (PMS2, MLH1, MSH2, MSH6) accounted for 1.74 percent of variants in the total population tested.

Genetic Risk of Prostate Cancer Underestimated, *from page 9*

"The importance of BRCA1/2 and other DNA repair genes outlined in the NCCN guidelines represents a small subset of the findings that would benefit patients with prostate cancer," write the authors. "Therapeutic implications of non-BRCA germline alterations remain unclear, but identification of positive variants in genes not included in the current guidelines have serious implications for treatment options, including clinical trials, particularly basket trials that examine specific genetic biomarkers regardless of tumor type."

The researchers also note that there was a "considerable lag" between the initial diagnosis of prostate cancer and referral for germline genetic testing across almost all age groups, although age at testing was not associated with the risk of finding positive variants. Further, family history of breast, prostate, ovarian, colon, pancreatic, or other cancers did not correlate with positive variant detection.

Gleason scores, which were available for 43 percent of patients, also were not associated with the presence of positive mutations.

There were significant differences in positive results seen by ancestry/ethnicity. The highest rates were found among Ashkenazi Jewish (22.7 percent) and white (17.8 percent) men. African Americans (10.1 percent) and Hispanics (6.4 percent) had significantly lower rates of positive variants.

Based on self-reported family histories, more than one-third of men (37 percent) with positive variants would not have been approved for genetic testing based on National Comprehensive Cancer Network recommendations. Additionally, only 43.8 percent of variants were detected in genes indicated for testing by the 2018 prostate cancer guidelines (BRCA1/2, ATM, PALB2, FANCA).

"Comparing the one-time cost of genetic testing to the high cost of treating catastrophic late-stage cancer in patients with a genetic risk that was not otherwise identified, as well as the benefit to family members from early screening, provides substantial justification for the simplification and expansion of current guidelines," conclude the authors.

Takeaway: Disease-causing variants are more common in men with prostate cancer than previously thought. Additionally, current genetic testing recommendations miss more than one-third of men with prostate cancer who test positive for pathogenic variants, suggesting that broader genetic testing guidelines are needed.

Blood Markers Alone OK For Surveillance With Some Pediatric Cancers

Tumor markers alone may be adequate to monitor for relapse among children and teens with malignant germ cell tumors (MGCTs), according to a study published online Dec. 21, 2018 in the *Journal of Clinical Oncology*. The authors say that eliminating routine CT scans from surveillance protocols for children who have elevated tumor markers at diagnosis could substantially reduce unnecessary radiation exposure and may enhance the safety of relapse surveillance.

Current pediatric North American MGCT protocols include CT scans of the chest, abdomen, and pelvis for surveillance following treatment, with repeat scans called

for quarterly for the first year, twice annually during the second year, and annually for up to 5 years post-treatment. However, there are concerns about significant cumulative radiation dose, particularly for cancer with such good prognoses.

The researchers retrospectively reviewed data for 284 patients enrolled in a phase III, single-arm trial for low-risk and intermediate-risk MGCTs in order to identify the method used to detect relapse (e.g., tumor markers, imaging, and/or pathology reports). Serial alpha-fetoprotein (AFP) and beta–human chorionic gonadotropin (b-HCG) measurements were used for tumor marker monitoring.

Over a median 5.3 years of follow-up, the researchers found that none of the seven patients who had normal tumor markers at initial diagnosis experienced a relapse. However, 48 patients with elevated tumor markers at diagnosis did experience a relapse. Nearly all (47 of 48) relapses were detected by tumor marker elevation, including 39 with elevated AFP elevation, one with elevated b-HCG, and seven with elevated levels of both tumor markers. One-third of patients (n = 16) had no reported site of relapse (normal imaging), with elevated tumor markers being the indicator of relapse, while two-thirds of patients had both abnormal tumor markers and imaging.

"If the 284 patients enrolled in this trial each had the nine CT scans prescribed by protocol for surveillance, they would have collectively undergone 2,556 CT scans of the chest, abdomen, and pelvis," write the authors led by Adriana Fonseca, M.D., from University of Toronto in Canada. "Using the estimates proposed by Miglioretti et al., that a radiation-induced solid cancer is projected to result from every 300 to 390 abdomen/pelvis CT scans and every 330 to 480 chest CT scans in girls, we appreciate the significant risks associated with this surveillance schedule, especially when nearly all patients could have had their relapse detected by tumor markers alone."

Takeaway: Tumor markers may be reasonable for primary surveillance following treatment for MGCTs for patients with positive tumor markers at diagnosis, thereby substantially cutting the number of CT scans needed for routine monitoring.

Current Metal Sensitivity Testing Not Adequate for Diagnosing Immune-Related Knee Replacement Failure

Metal sensitivity test results, including lymphocyte transformation testing (LTT), are insufficient to diagnose knee replacement failure due to an immune reaction, according to a study published Feb. 6 in the *Journal of Bone and Joint Surgery*. The authors say the findings highlight the need to establish diagnostic criteria for total knee arthroplasty (TKA) failure due to an immune reaction.

While TKA is usually successful, an estimated 20 percent of patients are dissatisfied due to chronic pain and/or stiffness, which can be a result of a local immune reaction to the metal. However a hypersensitivity reaction can be considered in cases with low prosthetic wear and a high aseptic lymphocyte vasculitis-associated lesion (ALVAL) histopathology score, however, it remains a topic of debate for how to definitively diagnose metal sensitivity test as the cause of TKA failure.

Previous research shows that while an estimated 10 to 15 percent of the general population is reactive to skin patch testing for metal sensitivity—most commonly, nickel—skin patch testing is not useful for predicting clinical results with TKA.

Current Metal Sensitivity Testing Not Adequate for Diagnosing Immune-Related Knee Replacement Failure, *from page 11*

It is important to understand the role of metal sensitivity in necessitating TKA revision surgery, as the average cost of the hypoallergenic revision implants is $5,669, or 37 percent more than the standard revision implants, the authors say. Additionally, LTT testing costs nearly $400 per patient.

The present study sought to characterize the relationship of a positive LTT result to histopathologic findings and clinical outcomes among patients undergoing TKA revision. All 27 patients (21 female; mean age, 64.0 years) had a negative infection work-up based upon erythrocyte sedimentation rate, C-reactive protein, and synovial fluid analysis and culture results. All patients had persistent pain and/or stiffness and underwent revision due to a suspected metal allergy to nickel, based on positive LTT results. Periprosthetic tissue samples (synovial tissue directly adjacent to the anterolateral flange of the femoral component) were collected at the time of revision surgery and were scored using the aseptic lymphocyte-dominated vasculitis-associated lesion (ALVAL) scoring system by a single blinded pathologist.

The researchers found that over an average of 3.6 years from primary to revision surgery, LTT results categorized eight patients as mildly reactive, eight patients as moderately reactive, and 11 patients as highly reactive to nickel. Additionally, one patient was moderately reactive and three were mildly reactive to cobalt, while one patient was moderately reactive and four were mildly reactive to chromium.

Routine histopathologic analysis predominately found fibrosis and varying degrees of lymphocytic infiltration in 63 percent of the cases, with an average ALVAL score of 3.1 out of 10, leading the authors to conclude the histopathology results were "generally nonspecific and nondiagnostic of an immune reaction."

Post-revision, knee function scores improved significantly. However, neither LTT stimulation index as a continuous variable nor as a categorical variable (mildly reactive, moderately reactive, highly reactive) was correlated with ALVAL score, pre-revision function, or change in function post-revision. Further, AVAL scores did not correlate significantly with either pre-revision or post-revision knee function.

"A distinction should be made between a positive LTT-diagnosed metal sensitivity and TKA failure due to an immune reaction," write the authors led by Steven Yang, M.D., from Harbor-UCLA Medical Center in Torrance, Calif. "A positive LTT result may not indicate that an immune reaction is the cause of pain and stiffness post-TKA."