News

Research Highlights

Third clinical trial reinforces the use of the GeneSight® pharmacogenomic test

A study published in a recent issue of *Discovery Medicine* is the third clinical trial to provide evidence for the effectiveness of the GeneSight® combinatorial pharmacogenomic test for selecting psychotropic medication.

The group from AssureRx Health, Inc. (OH, USA) conducted a prospective double-blind randomized control trial in order to evaluate the benefit of GeneSight, a five gene pharmacogenomic test and interpretive report. They used this information to manage psychotropic medications used in the treatment of patients with major depression.

The trial involved recruiting 51 patients from The Pine Rest Christian Mental Health Services (MI, USA) who were suffering from depression. These patients were randomly assigned to be treated as usual or in combination with GeneSight. Subjects were blinded to their treatment group and depression severity was assessed by blinded study raters. GeneSight works by categorizing patients by their genetic profile into green, yellow or red groups depending on their predictive response to certain medications.

The results of the trial showed that pharmacogenomic-guided treatment with GeneSight doubled the likelihood of a response in all patients with treatment-resistant depression. In addition GeneSight also identified 30% of patients with severe gene–drug interactions who had the greatest improvement in depressive symptoms when switched to genetically suitable medication regimens.

Bryan M Dechairo, Senior Vice President, Medical Affairs & Clinical Development at Assurex Health explained "The Pine Rest randomized control trial replicated and reaffirmed the clinical validity of GeneSight by prospectively categorizing and predicting which patients receiving current standard of care would have high, medium or low response to treatment using our patented combinatorial pharmacogenomic GeneSight test and actionable green, yellow and red medication stratification report."

> "The results of the trial showed that pharmacogenomic-guided treatment with GeneSight doubled the likelihood of a response..."

Joel G Winner, Medical Director at Assurex Health, said "The data in this paper align with our previous two published trials which show a doubling of response rate for major depressive disorder when the clinician uses GeneSight compared with those who did not use this integrated pharmacogenomic information." Winner concluded "To my knowledge, this is the first real-world, double blind randomized control trial for pharmacogenomic intervention in psychiatry, making it an invaluable addition to the psychiatric literature."

– Written by Theo Bond

Sources: Winner JG, Carhart JM, Altar CA, Allen JD, Dechairo BM. A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder. Discov. Med. *16(89), 219–227 (2013); Assurex Health press release: http://assurexhealth.com/third-clinical-study-confirms-treatment-guided-by-genesight-psychiatric-pharmacogenomics-test*

Future Medicine part of fsg

BRCA-negative women from *BRCA*-positive families may still be at increased risk of developing breast cancer

"We found that women who test negative for family-specific *BRCA2* mutations have more than four-times the risk for developing breast cancer than the general population," states Gareth Evans (University of Manchester, Manchester, UK), commenting on a recent study into the risks of breast cancer in individuals from families carrying the *BRCA* mutation, but who test negative for the family-specific mutation themselves. The results of the present study, published in *Cancer Epidemiology, Biomarkers & Prevention*, oppose the current understanding that those testing negative for *BRCA* mutations in a *BRCA*-positive family are at the same risk of developing breast cancer as the general population.

According to the National Cancer Institute (MD, USA), if a women tests negative for the family-specific *BRCA2* mutation but comes from a BRCA positive family she is considered to have the same risk of developing breast cancer as the general population. However recent evidence suggests otherwise.

The M6-Inherited Cancer in England study identified families with ovarian and/or breast cancer and screened for mutations in both *BRCA1* and *BRCA2*. This included information on the effected individuals as well as their relatives, which Evans and his colleagues then analyzed.

> "The results of the present study ... oppose the current understanding that those testing negative for *BRCA* mutations in a *BRCA*-positive family are at the same risk of developing breast cancer as the general population."

The investigators identified 49 women out of the 807 *BRCA* families who developed breast cancer despite testing negative for their family-specific *BRCA* mutations. The investigators subsequently referred to these women as 'phenocopies'. Twenty-two of these phenocopies were from *BRCA1* families with the remaining 27 being from *BRCA2* families. When stratifying the phenocopies by age (ranges 30–39, 40–49,

50–59 and 69–80 years) there were twice as many cases of breast cancer in each age range than would be expected in the general population.

To further investigate this risk, the researchers calculated a ratio for the 'observed risk for breast cancer in *BRCA*-negative women from *BRCA* families, versus the risk expected for any woman in the general population', called the O/E (observed vs expected) ratio. Phenocopies from the *BRCA1* families were found to not be at significantly higher risk of developing breast cancer than the general population, *BRCA2* phenocopies presented with a higher ratio however of 4.57. Evans and colleagues therefore concluded that the fourfold increase in risk presented by *BRCA*-negative women mostly impacts those from *BRCA2* families.

The results from this research oppose the National Cancer Institutes current statement on the issue. The authors therefore propose that providing women with a risk equal to that of the general population after a *BRCA*-negative result should be carefully considered, especially those women from *BRCA2* families.

– Written by Elizabeth Webb
Illustrated by Amy O'Donnell

Also featured on www.oncology-central.co.uk
Source: American Association for Cancer Research press release: www.aacr.org/home/public--media/aacr-in-the-news.aspx?d=3219

Acquired resistance mechanisms further characterized in melanoma

It is currently believed that approximately 40% of advanced melanoma tumors are driven by mutations in the *BRAF* gene. BRAF inhibitors have recently been demonstrated to promote a rapid antitumor response in the majority of patients with $BRAF^{V600}$-mutant melanoma. However, most of these individuals will eventually develop resistance to such therapy. Two studies published online last week in the journal *Cancer Discovery* provide key information concerning how melanoma tumors may be able to resist the action of BRAF inhibitors.

The studies, both carried out at the University of California's Jonsson Comprehensive Cancer Center, indicate key cell-signaling pathways utilized by melanoma to learn resistance to BRAF inhibitors and suggest the limited focus of the drugs themselves allow the cells to evolve and escape their action. Roger Lo (Jonsson Cancer Center) led the studies, which both investigated resistance to BRAF inhibitors in melanoma biopsy samples.

In the first of the studies, 100 patient biopsies from patients treated with BRAF inhibitors were analyzed in an attempt to elucidate the signaling pathways that contribute to BRAF inhibitor resistance. Lo believes that the carrying out these investigations at the molecular level provides a more robust view of the scale of the issue. This study concluded that BRAF-inhibitor resistant melanoma tumors utilize many signaling routes to gain resistance to therapies and that resistance routes can be multiple in some individuals.

> "The studies ... indicate key cell-signaling pathways utilized by melanoma to learn resistance to BRAF inhibitors..."

"By helping us understand the core resistance pathways and tumor heterogeneity, fitness and mutational patterns that emerge under drug selection, this study lays a foundation for clinical trials to investigate the mechanisms of tumor progression in *BRAF*-mutant melanoma patients," Lo commented.

The second of the studies established that melanomas are able to action a process termed early adaptive response upon exposure to BRAF inhibitors. This allows them to quickly initiate drug resistance pathways, which are then fortified and further activated over time allowing the cells to resume growth. The researchers believe their results indicate that the processes of early and late resistance to BRAF inhibitors are linked, although the mechanisms may differ. They state that discovering these core escape pathways is paramount when fighting BRAF inhibitor resistance in melanoma, as treatments could in theory be designed to block all such pathways upon initiation of therapy. Such treatment could result in a longer period of tumor shrinkage or potentially even eradication.

"We now have a landscape view of how melanoma first adapts and then finds ways to overcome what is initially a very effective treatment," explained Antoni Ribas, also of the Jonsson Cancer Center, coinvestigator on both studies. "We have already incorporated this knowledge into testing new combination treatments that we hope will get us back ahead of melanoma and not allow it to escape the initial treatment effectiveness and return."

– Written by Emily Brown

Also featured on www.oncology-central.co.uk
Sources: Shi H, Hugo W, Kong X et al. *Acquired resistance and clonal evolution in melanoma during BRAF inhibitor therapy.* Cancer Discov. *4(1), 80–93 (2013) (Epub ahead of print); University of California, Los Angeles press release: www.newsroom.ucla.edu/portal/ucla/cancer-researchers-translate-new-249384.aspx?ncid=5367*

Previously unknown side effect of crizotinib emerges

Crizotinib is a drug that is used to treat ALK-positive non-small-cell lung cancer. It was fast tracked by the US FDA owing to its superior efficacy, yet at the time less was known about its side effects. This can be attributed to the shorter period of time in which crizotinib transitioned from bench to bedside compared with other drugs. Owing to this, some side effects of the treatment are still only just presenting in patients. Researchers from the University of Colorado Cancer Center (CO, USA) have found that kidney function is decreased in patients taking crizotinib. It is uncertain as to whether this is due to the drug itself or the accuracy of the clinical method used to assess the kidney function. As well as kidney function, the researchers found that testosterone levels were reduced in 84% of male patients.

Using a simple creatinine test, the glomerular filtration rate (GFR) of 38 patients with stage IV ALK-positive non-small-cell lung cancer being treated with crizotinib was investigated. The mean GFR dropped by 23.9% in individuals being treated with crizotinib, particularly in the first 2 weeks, and then leveled out. For the 16 patients for whom post-treatment information was available, the GFR rates recovered to within 84% of their original rate. For individuals with a healthy GFR before treatment, the change in GFR may not be outside the normal range; however, if a patient has kidney problems or damage and is administered crizotinib, the drug will worsen their condition, and they should be taken off the drug.

Lead author Ross Camidge (University of Colorado Cancer Center) commented: "as anticancer drugs enter the pharmacy quicker and quicker, we have to empower the hundreds and thousands of doctors out there to believe in what they might see in their clinics and report things, leveraging all that experience for the greater good. In the cases of altered measures of kidney function and lowered testosterone with crizotinib, once we notice these side effects and get the word out, patients can be much more appropriately managed."

Elucidating the mechanism of the kidney damage is now the focus of this research. The rapid onset but quick recovery of the change in GFR suggests that crizotinib is not causing permanent kidney damage. Camidge explained that: "We are doing extra studies, but the jury remains out on the exact mechanism. However, because an interference with the validity of creatinine for assessing kidney function is still a possibility, if a patient's creatinine seems to heading into some kind of danger zone on crizotinib, and a doctor is considering altering their management of the patient, we would strongly recommend reassessing kidney function through a second, noncreatinine based, method before making any final decision."

– Written by Emily Hargrave

Also featured on www.oncology-central.co.uk

Source: Brosnan EM, Weickhardt AJ, Lu X et al. *Drug-induced reduction in estimated glomerular filtration rate in patients with ALK-positive non-small cell lung cancer treated with the ALK inhibitor crizotinib.* Cancer *doi:10.1002/cncr.28478 (2013) (Epub ahead of print).*

About the News & Views

The News & Views highlights some of the most important events and research in the field of pharmacogenomics.

If you have newsworthy information, please contact:

Sarah Jones, Commissioning Editor, *Pharmacogenomics*,
Future Medicine Ltd, Unitec House, 2 Albert Place, London, N3 1QB, UK;
Tel.: +44 (0)20 8371 6090;
s.jones@futuremedicine.com