News

Research Highlights

# Healthy genome sequenced to predict risk of disease and response to treatments

*Study hopes to propel the use of personal genome sequencing out of the laboratory and into routine clinical practice*

With the falling costs of DNA sequencing techniques, interest in personal genomics has increased substantially. A recent study, carried out by investigators from Stanford University School of Medicine (CA, USA), set out to sequence the entire genome of a healthy patient with the aim of using the data obtained clinically. The paper reporting their interesting results was published in *The Lancet* on the 1st May 2010.

> "*...whole-genome sequencing can yield useful and clinically relevant information for individual patients.*"

A patient with a family history of vascular disease and early sudden death was chosen as the 'healthy genome' to be sequenced. First, the patient was assessed clinically to predict the risk for coronary artery disease and was screened for any causes of sudden cardiac death. This was then followed by the analysis of the patient's full genome sequence, accompanied by genetic counseling. The investigators developed new methods for the integration of whole-genome and clinical risk data. Dr Euan Ashley, Assistant Professor of Medicine, commented that, "The challenge lies in knowing what to do with all that information. We've focused on establishing priorities that will be most helpful when a patient and a physician are sitting together looking at the computer screen".

Once they had sequenced the patient's entire genome, they analyzed the 2.6 million single nucleotide polymorphisms and 752 copy number variations that were found. From all the genetic data, they elucidated that the patient had an increased genetic risk for myocardial infarction, Type 2 diabetes and some cancers. They also discovered rare variants in three genes that are clinically associated with sudden cardiac death – *TMEM43*, *DSP* and *MYBPC3*. A variant in LPA was consistent with a family history of coronary artery disease. The patient was also found to be heterozygous for a null mutation in *CYP2C19* suggesting resistance to the drug, clopidogrel. They also found that the patient harbored several variants associated with a positive response to lipid-lowering therapy, as well as specific genetic variants present in the *CYP4F2* and *VKORC1* genes, suggesting that the patient might have a low initial dosing requirement for warfarin. There were also many variants of unknown importance that were also reported to occur in the patient.

The authors concluded their study by stating that although many challenges remain, their results suggest that "whole-genome sequencing can yield useful and clinically relevant information for individual patients".

The ethical and practical challenges of the research was discussed in an accompanying article also published in *The Lancet*, authored by some of the investigators involved in the study along with Prof Hank Greely, director of Stanford's Center for Law and the Biosciences, as the senior author.

*Sources: Ashley EA, Butte AJ, Matthew T* et al.*: Clinical assessment incorporating a personal genome.* Lancet *375(9725), 1525–1535 (2010); Ormond KE, Wheeler MT, Hudgins L* et al.*: Challenges in the clinical application of whole-genome sequencing.* Lancet *375(9727), 1749–1751 (2010).*

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# US FDA approves first fully automated blood test for Chagas disease

The US FDA has approved the Biological License Application for the ABBOTT PRISM Chagas test, the first fully automated blood screening assay for Chagas disease. The assay detects antibodies to the parasite, *Trypansoma cruzi*, which is found exclusively in the Americas and most frequently transmitted through contact of the feces of an infected triatomine, more commonly know as the kissing bug. Infection can also occur through transfusions of contaminated blood or organs from an infected donor; the assay is also able to test serum and plasma specimens and has the potential prevent infection through such means.

Chagas disease, if left untreated, can be fatal and it is estimated that up to 11 million people are infected worldwide each year, with an additional 108 million or more at risk. National screening for Chagas disease began in 2007 and since then more than 1000 cases of the disease have been identified.

John Coulter, Divisional Vice President, US commercial operations, Abbott Diagnostics, commented that, "The approval of the ABBOTT PRISM Chagas test marks the availability of an important automated tool to ensure the continued safety of our blood supply, and it also offers our customers the ability to conduct all their serology testing on one system to increase the productivity and efficiency of their labs."

The approval of the new screening assay is the last in Abbott's range of blood screening tests, which also includes assays for hepatitis and HIV, and will be an important tool in tackling one of the world's neglected tropical diseases.

*Source: http://www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0858.htm*

# Novel biomarkers predict resistance to endocrine therapy in breast cancer

Researchers at University College Dublin, Ireland, have identified two new biomarkers that indicate resistance to endocrine therapy in breast cancer patients. These biomarkers could lead to the development of prognostic tests that could also help decide which therapies will be most effective for a particular tumor.

Endocrine therapy, a treatment that involves removal or replacement of hormones, is one of the most effective treatments for breast cancer. However, 40–50% of patients with estrogen receptor-positive breast cancers still relapse following this treatment. Estrogen receptor and HER2 analysis have increased clinicians' ability to predict who will benefit from endocrine therapy. Nevertheless, resistance to endocrine therapy is still poorly understood.

> *"...this research will provide vital information about drug resistance to ensure that people with breast cancer are getting treatments that will benefit them."*

Researchers at University College Dublin have discovered a novel pathway of resistance to endocrine therapy. In this study, they used a proteomics-based approach to identify proteins that are associated with the endocrine-resistant phenotype. In particular, two proteins that interact in the same pathway were identified: HOXC11, a transcription factor of the homeobox family of proteins; and SRC-1, the steroid-receptor coactivator protein. These two proteins cooperate to regulate expression of the calcium-binding protein S100β in resistant breast cancer cells.

Nuclear HOXC11 and S100β were found to predict poor disease-free survival in breast cancer patients and these proteins could be detected in the blood. The UK based charity Breast Cancer Campaign is funding further work on this project with the aim of developing new blood tests to predict which patients will benefit from which therapies. Leonie Young, the lead researcher on the project, hopes that "this research will provide vital information about drug resistance to ensure that people with breast cancer are getting treatments that will benefit them."

*Source: http://www.medicalnewstoday.com/articles/189876.php*

# Cofilin expression levels serve as an indicator for lung cancer progression risk and response to treatment

Non-small-cell lung cancer (NSCLC) is a serious, widespread form of cancer for which chemotherapy is generally poorly personalized at present. This may change, however, following the results from a study led by Dr Fábio Klamt (Federal University of Rio Grande do Sul, Brazil).

Non-small-cell lung cancer is known for producing early metastasis, a property that requires substantial motility on the part of the cancer cells. Therefore, Klamt's group decided to focus on the *CFL1* gene – a known member of the metastasis pathway that codes for the actin-remodeling protein cofilin – as a possible NSCLC biomarker. Klamt explained this decision; "cofilin is a protein associated with cell mobility. We know that poor prognosis correlates with the ability of cells to move to generate metastasis. Thus, it seemed only reasonable that cells with lower levels of this protein would be less aggressive while higher levels would provide a more aggressive behavior".

Initially examining samples from 111 NSCLC patients, the study went on to compare six cell lines with differing levels of *CFL1* expression *in vitro*. The data from these analyses indicated that higher levels of cofilin were associated with an increased potential to invade different parts of the body, leading to metastasis.

As well as this finding concerning cell mobility, it was found that high levels of cofilin were associated with resistance to chemotherapy, including the standard first-line treatment, cisplatin. This discovery indicates that many individuals may be assigned to a therapy that has little chance of success in their particular case, something that will hopefully change as a result of this research.

*Sources: Castro MAA, Dal-Pizzol F, Zdanov S* et al.*: CFL1 expression levels as a prognostic and drug resistance marker in nonsmall cell lung cancer.* Cancer *(2010) (Epub ahead of print); Publicase press release: www.publicase.com.br*

> "*This discovery indicates that many individuals may be assigned to a therapy that has little chance of success in their particular case, something that will hopefully change as a result of this research.*"

# Multiplex PCR testing for respiratory viruses receives boost

A recent study has demonstrated that multiplex PCR tests outperform conventional diagnostic tests for respiratory viruses. This supports a growing body of evidence that multiplex PCR diagnostic tests should be used with more confidence in a clinical setting.

In the study, researchers from the Washington University School of Medicine (USA) compared the PLx MultiCode® Respiratory Virus Panel (PLx-RVP) with the more conventional test methods of fluorescent antibody staining and fibroblast tube cultures.

The PLx-RVP, manufactured by Eragen® (Madison, WI, USA), uses an expanded genetic alphabet, multiplex PCR chemistry and microsphere flow cytometry to rapidly and specifically detect respiratory viruses directly in clinical specimens.

The unique feature of the MultiCode technology is an expanded genetic alphabet that includes two synthetic bases, known as isoC and isoG. This is similar to the natural DNA base pairs, isoC and isoG, which are specific to each other and do not pair with any of the four natural bases. These synthetic bases allow higher specificity of detection than other nucleic acid-based assays.

The study consisted of 410 respiratory specimens, mostly nasopharyngeal swabs, of which 210 tested positive for a selection of common respiratory viruses by conventional testing. The accuracy was confirmed using reference PCR assays and nucleotide sequencing where possible. Overall, it was found that PLx-RVP increased the total detection of viruses by 35.85% with a 25.7% increase in positive specimens.

The sensitivity of the PLx-RVP ranged from 94 to 100% and the specificity from 99 to 100%, depending on the individual virus. In particular, the test performed better than traditional methods for the detection of rhinoviruses, as well as having the added capability of detecting metapneumovirus and human coronaviruses.

The authors concluded that "PLx-RVP is a highly accurate method for the detection of respiratory viruses and significantly improves the detection of these viruses compared to conventional virologic testing." Moreover, Gregory Storch, corresponding author on the paper published in the *Journal of Clinical Microbiology*, said he sees the panels as "a huge development in diagnostic microbiology."

*Sources: Arens MQ, Buller RS, Rankin A* et al.*: Comparison of the Eragen Multi-Code Respiratory Virus Panel with conventional viral testing and real-time multiplex PCR assays for detection of respiratory viruses.* J. Clin. Microbiol. *48(7), 2387–2395 (2010); www.eragen.com; www.genomeweb.com/pcrsample-prep/recent-studies-prop-multiplex-pcr-testing-respiratory-viruses*

# Simple gene tests are best for subtyping breast cancer

At the IMPAKT Breast Cancer Conference in Brussels (Belgium), US researchers reported that a simple test involving only three genes is among the most effective means of classifying breast cancer into subtypes.

Subtypes of breast cancer have distinct genetic profiles which mean that they may respond differently to treatment. "It is these differences that explain, at least in part, why patients who have tumors that appear to be similar, may experience completely different clinical outcomes, such as prognosis and response to anticancer therapies," said Dr Benjamin Haibe-Kains from Dana-Farber Cancer Institute (Boston, USA). "Thus, there is an urgent need for developing a robust tool to provide clinicians with guidance for classifying breast cancer molecular subtypes, which could then aid in making therapeutic decisions."

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With this need in mind, Dr Haibe-Kains and colleagues performed the largest comparative study to date of breast cancer subtypes. They analyzed 32 publicly available gene-expression datasets that included more than 4600 breast cancer patients.

In particular, the researchers were looking to rate different models for classification into subtypes. Two main types of classification model have been introduced over the last decade: the single sample predictor (SSP) and the subtype classification model (SCM). Refinement of these models has led to the publication of six distinct classification models, which were analyzed by the researchers.

"We studied these models in terms of concordance and prognostic value and, for the first time, we estimated their robustness: that is, their capacity to assign the same tumors to the same molecular subtypes whatever the gene expression data used to fit this model."

It was found that SCMs generally yielded more reliable results than SSPs. This was even the case when an SCM involving only three genes (*ESR1*, *ERBB2* and *AURKA*) was used compared with SSP models.

Dr Haibe-Kains concluded that, "the robustness of SCMs makes them promising candidates for an implementation into the clinic especially in the simplest form – that is, a model using only three genes."

*Source: http://www.sciencedaily.com/releases/2010/05/100506112559.htm*

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