Interview

Advancing personalized medicine to improve health outcomes

Amalia Issa is the founding Director of the Program in Personalized Medicine and is currently Associate Professor of Pharmacological and Pharmaceutical Sciences at the University of Houston (TX, USA). She has developed a unique area of translational research focused on pharmacogenomics and personalized medicine and how applications of personalized medicine will be translated and integrated into healthcare delivery and health systems. Issa was among the first scientists to publish papers on translational research and health policy issues related to personalized medicine and she is internationally recognized in this field.

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You have been in the field of personalized medicine for over a decade and founded the Program in Personalized Medicine & Targeted Therapeutics. How do you think personalized medicine has evolved over the past decade? What are some of the most important research milestones that have been reached?

There has been a tremendous degree of progress on several fronts in this field. This is readily evidenced by the exponential rise in publications since the beginning of the decade. There have been over 500 publications dealing with personalized medicine in the last 2 years alone. The growth in knowledge, technological advances and tools, particularly those ending in the 'omics', have basically exploded and have contributed to our collective understanding of the pathogenesis and management of a number of common diseases with complex etiology. There has also been an explosion in the existence of and access to whole-genome data that is available to scientists. On the regulatory front, advances in regulatory practices at the US FDA, the European Medicines Agency (EMA [London, UK]), Health Canada (Ottawa, Canada) and other organizations have also contributed to advancing the field. The FDA, in particular, has taken a proactive role in developing guidelines for pharmacogenomics and the development of relevant biomarkers and companion diagnostics for targeted therapeutics. More examples of personalized pharmacotherapy are now

available than ever before. Notable examples include drugs therapies in oncology such as Iressa®, Herceptin® and Erbitux®, of course, but pharmacogenomic information is also becoming integral to drug therapies for other indications, including Ziagen® and warfarin. So the regulatory agencies are clearly moving forward, adding pharmacogenomic information to drug labels, and in some cases, relabeling already approved drugs. This was the case in August 2007 when the FDA relabeled warfarin to include information regarding genotyping for *VKORC1* and *CYP2C9* to assist clinicians in improving their initial estimates of dosage requirements.

So, there is plenty of evidence, on a number of fronts for progression in the field of personalized medicine.

What are the main areas of research that you are involved with?

The key question that drives our research is: what is needed for the pharmacogenomics approach to personalized medicine to become well-integrated into clinical practice and effectively incorporated into healthcare delivery and health systems? Working towards this goal, we have a number of irons in the fire.

We are evaluating the clinical utility of genomic diagnostics and targeted therapeutics and the willingness of various patient populations (including cardiovascular disease, breast and colorectal cancer patients) to adopt and use genomic diagnostics for tailoring drug prescribing, including the willingness-to-pay for novel genomic diagnostics. We are addressing the questions of who will have access to genomic

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diagnostics and targeted therapeutics, what approaches patients opt for for testing and treatment and why (i.e., how they trade-off among the decisions they need to make and the impact on patient outcomes), and where genetically-based approaches will have the most value to patients and families. We are also interested in understanding which healthcare providers will use genotyping-guided prescribing and adopt personalized medicine applications, and what the barriers and facilitators are for adoption. We are also modeling the use of pharmacogenomics to identify adverse drug reactions in clinical trials. We can describe the statistical power of several approaches to identifying genetic variants in studies using clinical trial populations and, we have been comparing the statistical considerations for Phase II–III trials versus postmarketing (Phase IV) studies.

What essentially led to your interest in personalized medicine and health policy specifically?

In graduate school, while working on my PhD in neuropharmacology at McGill University (Montreal, Canada), I initially became interested in how basic science and clinical research discoveries are translated into real-world applications for clinical practice and to improve health outcomes. I was also fascinated by the problem of how variable the pace of knowledge translation is, and why some discoveries become, in a sense, accepted into mainstream clinical practice quite rapidly while others, despite seeming to be breakthroughs of significance, do not.

At the time, my interests focused on Alzheimer's disease, and then a colleague, Judes Poirier (McGill University) and his laboratory, demonstrated that apolipoprotein E genotyping could be used to stratify responders to tacrine in Alzheimer's disease trials. This led to me thinking up a series of questions about how we might use genotyping for drug response to improve health outcomes, and what might be the facilitators and barriers to translating and implementing this emerging field of pharmacogenomics and personalized medicine appropriately into clinical practice and healthcare delivery. At that time, in the 1990s, hardly anyone was really concerned

with the 'big picture' policy relevant questions. It was evident to me that the clinical integration of pharmacogenomics and applications of personalized genomic medicine would happen at a variable pace depending upon the particular application, and that this space needed to be investigated rigorously. I was fortunate that right after my PhD I received a grant from the Alzheimer Society of Canada (Toronto, Canada) to investigate issues related to genotyping in Alzheimer's disease.

Since few developments in healthcare have a greater impact on patients, providers and payers both now and in the foreseeable future than new pharmaceuticals, and genomic diagnostics and companion drugs that are currently available, as well as those in the pipeline will undoubtedly influence all areas of healthcare, it is critical to continue to conduct innovative research to inform health policy related to personalized medicine, in order to transform healthcare and health delivery systems.

What are some of the main issues in personalized medicine that your research is trying to tackle?

- The health system facilitators and barriers for the adoption of personalized medicine applications into routine clinical practice and healthcare delivery. We are interested in understanding the issues at all levels: from patients to providers, to the diagnostic laboratories, to regulatory practices and systems infrastructure issues.
- We are interested in the utilization and outcomes of particular personalized medicine applications.
- We are also interested in how pharmacogenomics might be used to enhance drug safety efforts.

Just to name a few things.

How far do you think we are to realizing the potential of individualized healthcare in the clinic?

We are already realizing personalized genomic medicine clinically, at least in some areas of medicine. The question is, how will the collective infrastructure of

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health systems and healthcare delivery need to change in order to better integrate personalized genomic medicine as an integral part of routine clinical practice? Although many people think of this in terms of IT issues, including electronic medical records, the infrastructure issues are actually more complex. For instance, how will diagnostic laboratories need to be restructured to accommodate the more routine use of genomic diagnostics?

Adverse drug reactions are a major problem. Can the implementation of genetic analysis into clinical trial methodology help to alleviate them?

There is definitely an urgent need to develop strategies to reduce the problem of adverse drug events and improve the effectiveness of pharmaceutical products. But these strategies and processes have to occur at multiple levels, including at the level of regulation as well as that of the pharmaceutical industry. With respect to clinical trials, first of all, it is important to recognize that there are many factors contributing to adverse drug reactions, such as drug–drug interactions and certain environmental characteristics, including those related to diet. This is important to keep in mind when considering the processes and strategies that will be necessary to implement and improve drug safety. That being said, pharmacogenomics and the implementation of genetic analysis could provide benefits by, for example, stratifying human subjects in a trial by genotype. But we will have to collectively develop valid methodologies, including statistical techniques and appropriate regulatory standards, before we can do this on a more routine basis.

What, in your opinion, are some of the major challenges at the moment that hinder personalized healthcare from moving forward?

As with anything that is still an emerging field, many challenges exist at multiple levels. One of the key bottlenecks right now, is the need to clinically validate biomarkers and, what I like to call, ‘genomic diagnostics’ as predictors of therapeutic

outcome. And that is for those markers that have been established! In addition, we still need to carry out major preclinical discovery work to determine which genetic variants regulate which explicit pharmacological effects. Without this information, we do not have a clue which biomarkers are clinically useful. As we continue to amass this data, we will also need rigorous studies to demonstrate that we can indeed appropriately associate probabilistic risk information with specific variants and, equally importantly, that we can use this information in such a way that will lead to improved health outcomes. So, there is a need for research into the utilization and outcomes of this arena. This naturally leads to another important challenge – how to convey probabilistic risk information to patients so that they understand it and are able to use it to make decisions for themselves. This notion of interpreting probabilistic risk information is not new or only particular to genomics and personalized medicine, but it is going to become much more important.

Finally, there are also a host of socio-economic issues that present with challenges as well and these vary from country to country. For example, here in the USA, figuring out the coverage and reimbursement issues is huge.

How can personalized medicine change the face of healthcare as we know it?

As personalized medicine continues to evolve, it will change healthcare delivery as we currently know it. There are several potential ‘game changers’ that are likely to have a significant impact on the delivery of healthcare. On the technology front, we may be moving towards portable DNA scanners, much like we see in shopping nowadays, only in this case, they would be available to physicians for use in their offices with a few drops of blood from a patient. Another technology that we will see is the evolution of the microarray chip to the point where it can be used to detect markers and facilitate monitoring. Beyond these technological game changers, and possibly several others, we will see game changers that are relevant to the infrastructure of healthcare delivery. That is, assuming that personalized genomic

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medicine becomes far more routine than it currently is, we are likely to see a re-engineering of the health insurance industry, particularly in how we currently think about reimbursement. The diagnostics and pharmaceutical industries are likely to undergo a restructuring as well, from the prevailing model of blockbuster drugs that we have seen to date, to a different drug development and economic model, to incorporate drugs that are targeted to smaller subpopulations based upon genotyping algorithms.

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