INTERVIEW

THE ZEAL OF THE RECENTLY INITIATED

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AFTER RETRAINING AS A MEDICAL GENETICISTS, ROBERT GREEN HAS NEVER LOOKED BACK. TODAY, HE IS ONE OF THE LEADING LIGHTS IN THE JOURNEY TOWARDS GENOMIC MEDICINE.

Those of you who made it out to the very first Festival of Genomics in Boston last summer, will probably remember Robert Green for his brilliant turn as chairman on the main stage. He is one of the most recognisable faces in the field, and is involved in several ground-breaking projects. We were fortunate enough to book some time in his demanding schedule to find out how he found his way into the exciting world of medical genetics.

FLG: Your CV is impressive in the scale and the quantity of achievements and projects that you are currently involved with. I think it's safe to say that you are one of the main forces driving us towards an era of genomic medicine. When did you first decide that medicine and indeed medical genetics was what you really wanted to devote your professional life to?

RG: Well my story is unusual in that I began my career in neurology and ended up specialising in the area of Alzheimer's disease. Gradually over the years of working in that area I became convinced by the data that Alzheimer's disease was a genetic illness, and as that became clear I ended up working in genetic epidemiology of Alzheimer's disease looking at environmental and genetic risk factors, including helping to lead one of the largest family studies of Alzheimer's disease that had been conducted at the time as well as a number of clinical trials in treatments for Alzheimer's disease that were unfortunately not successful.

This experience in epidemiology, genetic epidemiology and clinical trials was critical for the next phase of my career. At about this time in the 1990s APOE was identified as a genetic risk factor for Alzheimer's disease, and I got very interested in the question of whether family members who wished to know their APOE genotype would be in some way harmed or potentially even helped by learning this information. At that time the prevailing opinion, expert opinion to some degree, was that it was not advisable to share such information with people since there was no medical treatment available for Alzheimer's disease. But this really seemed wrong, to not allow people to have knowledge about themselves if they really wanted it.

So late in the 1990s we began a series of randomised clinical trials called the Risk Evaluation and Education for Alzheimer's disease (REVEAL) Study, in which we examined, in a very rigorous way, what the impact of disclosing APOE for risk of Alzheimer's disease to people who want to learn that information was. We ended up being funded for 15 years in a series of four separate randomised clinical trials involving over a thousand individuals, and our major conclusions were that among people who truly wanted this information, there appeared to be no actual harm and a number of benefits from learning the information even though there were no medical treatments at the time. And so in the course of the REVEAL Study we helped coin the term 'personal utility', and we examined in some detail people's perceptions, reactions, recall and importantly their medical, behavioural and economic outcomes associated with learning about genetic risk information.

I was then so excited about the promise of genetics in medicine that I stepped away from my position as a full professor of neurology and retrained as a resident in medical genetics. With the knowledge and experience that I gained through that training we expanded our empirical studies in translational genomics into direct-to-consumer testing and genome sequencing in adults and new-borns.

FLG: Genomic medicine is something that you've really thrown yourself into. Is there anything else you can see yourself having picked as a career that you would have been just as passionate about?

RG: Well, early in my career I was passionate about neurology and cognitive neurology, but in my mind the brain and the genome are both two of the most exciting frontiers in the future of medicine. So, it just seemed natural for me to transfer my enthusiasm for neurology and cognition through the venue of epidemiology and clinical trials into this new arena of genomic medicine. I come to it later in my career than most, but with the zeal of being recently initiated!

FLG: As well as being responsible for a tremendous amount of work behind the scenes, you're also one of the public faces of genomic medicine. How important is it to keep the general public informed about genomic medicine, and how do you tailor your message, so that it's not only something that will excite people, but also be grounded in what is realistic?

RG: Well, part of the skill set in epidemiology and clinical trial research that I accrued over the years was based on public health training. And one of the challenges of public health training is that it is extremely important to engage with society also on an educational level and a policy level. If we do our academic work in isolation we are likely to have much less influence on the course of events as they unfold. I don't think it's an exaggeration to say that genomics is a truly revolutionary set of technologies that will disrupt and change the practice of medicine in ways that are profound and that reach not only into the practice of medicine but the business of medicine, the business of biotechnology, policy concerns and decisions throughout our country and throughout the world.

So for all those reasons I think it's critical that we, in science, be active in articulating the highest principles of scientific evidence, of sound policy and represent a, particularly in academic medicine, responsible voice in the series of activities that is occurring around this topic.

FLG: Whenever we ask people what they feel needs to happen to progress genomics medicine, we often get told about the need to educate physicians. This is something that you have a very active role in yourself. As well as publishing extensively, you're also the Principal Investigator on the MedSeq project. How much have you learned about the task ahead from participating physicians and their patients in that project?

RG: Well, the education of the medical workforce around genomics is something that's been recognised as a critical element for quite a while by many people, and tremendous progress has been made by the National Human Genome Research Institute, by the organisation formally known as NCHPEG (National Coalition for Health Professional Education in Genetics) now operating out of the Jackson Lab, by the American Society for Human Genetics and by the American College of Medical Genetics and Genomics. So, there is a tremendous amount going on. But through our research in translational genomics we have been conducting actual clinical trials where regular doctors are provided with what we hope is appropriate orientation, and then given genomic information about their actual patients. We are studying how well they understand this, how well they communicate with their patients about genomic information, what the downstream medical orders are, doctor and patient behaviours, and economic costs to society that accrue from this kind of integration. So, what I'm most proud of in our work is that we're not speculating or providing opinions about this very important area, we are actually implementing genomic medicine with both specialists and non-specialists, and we are measuring the actual outcomes.

FLG: Do you see many near-term benefits from direct-to-consumer genetic testing? It seems to be quite a divisive issue for people at the moment.

RG: Direct-to-consumer genetic testing was very controversial when it launched, because of concerns that customer misunderstanding could lead to inappropriate medical action, false reassurance or added medical expense without particular benefit. There have now been over a million individuals around the world who've purchased direct to consumer genetic testing, there have been a number of very vigorous studies of customers of direct to consumer testing, including one of our NIH studies. While these questions remain and have not been definitively answered, the bulk of the evidence suggests that customers understand quite well what they're getting, they do not act inappropriately in ways that are medically or psychologically harmful to themselves, and that there is modest increase in cost of downstream medical care associated with receiving this information. It's hard to evaluate, in the short term, whether it is beneficial or not in terms of their actual health. What we do seem to see is a tremendous interest on the part of customers in both their medical genetics, their trait genetics and their ancestry, and a very strong point of view that people should have the right to have and explore their own genetic information if they would like to.

FLG: Do you often find that that's the view point of healthy individuals who are consulting their genetic information out of pure interest rather than seeking a diagnosis?

RG: First I think it's important to point out that none of us are permanently healthy. We have all suffered from some illness, are suffering from some illness, or will suffer from some illness in our life, many of those with genetic influence. Because people are so deeply interested in their own health, in maintaining their own wellness and in avoiding future illness, the appeal of medical genetics to ostensibly healthy people is tremendous. They're curious about things that are running in their family, they're curious about things they might have had before, they're curious about the conditions that they're struggling with, and they're very curious about anything they might encounter in the future. Certain individuals, who you might characterise as health information seekers, are very interested and very strongly advocate that they should have the right to obtain this information and explore it is they so choose.

FLG: As well as genomic data we're also starting to collect and record the hugely diverse range of phenotypic data and taking things like advances in smart phones and sensors. And when you add an electronic medical record, that's an impressively rich and deep data pool that we're looking at that might help provide better treatments for patients. Making the most of all of that requires an overhaul of IT infrastructures and even the way that we think about medical practice. How far away do you think we are from being able to actually pull all of these different data sources together to influence patient diagnosis and treatment? →

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Robert C. Green, MD, MPH is a medical geneticist and physician-scientist who directs the G2P Research Program (genomes2people.org) in translational genomics and health outcomes in the Division of Genetics at Brigham and Women's Hospital and Harvard Medical School. Dr. Green is internationally recognized for designing and conducting empirical studies in genomic medicine. He led the first experimental trials disclosing common complex disease risk (the REVEAL Study), one of the first prospective studies of direct-to-consumer genetic testing services (the PGen Study) and was lead author on influential recommendations for incidental findings in clinical sequencing from the American College of Medical Genetics and Genomics. He currently leads and co-leads the MedSeq Project and the BabySeq Project, respectively, two NIH-funded randomized trials designed to explore the medical, behavioral and economic implications of integrating genome sequencing into the medical care of adults and newborns.

RG: I think we are right here. I think we're there. I think that it's one of these situations where we must continue to collect data to refine our understanding of how to put these diverse data sources together and how to use them appropriately in the care of patients. But it is a long-term iterative enterprise, which has begun, and is already influencing the lives of patients. Now this is currently being done through biobanks and large healthcare systems, often funded by NHGRI and NIH, with such projects as the Clinical Sequencing Exploratory Research Consortium and the eMERGE consortium. And this is exploding now into its latest form with the launch and tremendous enthusiasm around President Obama's Precision Medicine Initiative and the NIH activity to implement that. As you know, that proposes to generate a one million person cohort that integrates phenotype information through the electronic medical record and a variety of biomarker information, including genomics, into an enormously rich research resource. And at the same time, without waiting years for all the various conclusions of that research, judiciously make elements of that dataset available, both in the aggregate and to individuals who are participating in those cohorts.

So, you know, I think this is underway predominantly in the research realm and it is expanding in such a way that it is going to gradually be part of medical care as part of the electronic health record and the integration of multidisciplinary information including genomics into improving the care of patients.

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FLG: You've been NIH funded for 26 years continuously and published over 300 papers, how have you seen genomic medicine develop in that time and is there one thing in particular you'd like to be remembered for in your career?

RG: Well, the academic enterprise is a skill set like anything else and I've been fortunate to be funded by NIH and to have the opportunity to disseminate our findings through the years. Of course it's not the number of papers that you write, it's the impact and that your scientific findings have on the world that really makes this an exciting job.

I would say that I am most excited about contributing to the integration of genomics, to the responsible integration of genomics into the practice of medicine, and into society as a whole. I was very proud to help lead the working group of the American College of Medical Genetics and Genomics that came with the first recommendations for searching and disclosing secondary findings in people who are being exome and genome sequenced. I'm very pleased that these recommendations have been taken up as a foundational policy for most molecular laboratories at this point in time; that these recommendations have served as a starting point for a wide range of conversation around return of research results in large scale research involving the volunteers who provide genomic information. So, I hope that I have additional discoveries to make in the area of penetrance and downstream medical behavioural economic outcomes of using genomics. But up to this point in time I would say I'm probably proudest of our work in secondary findings. ■