Inside AJHG: A Chat with Alan Beggs

January 17, 2019 ASHG News

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Each month, the editors of *The American Journal of Human Genetics* interview an author of a recently published paper. This month we check in with Alan Beggs to discuss his paper 'Interpretation of Genomic Sequencing Results in Healthy and Ill Newborns: Results from the BabySeq Project'.

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Several members of the BabySeq research team, including (L to R) Katie Dunn, Casie Genetti, Ingrid Holm, Alan Beggs, Robert Green, and Pankaj Agrawal. (courtesy of Dr. Beggs)

AJHG: *What prompted you to start working on this project?*

Alan: It is well established that genomic sequencing of individuals with a likely genetic disease has clear and recognized benefits that easily outweigh the risks and costs. However, we are just beginning to appreciate the potential benefits and costs of prospectively sequencing healthy individuals. There is a lot of hope around the prospects for disease prediction, presymptomatic diagnosis, carrier detection, pharmacogenomics and other potential benefits of genomic sequencing, and an equal amount of concern around the risks of misuse of genetic information, misinterpretation of probabilistic results or negative personal impacts such as anxiety, increased family stress or loss of trust that such information might engender.

The NIH Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT) program was conceived to explore the implications, challenges, and opportunities of genomic sequencing in the newborn period. Together with our colleagues here in

Boston, and in Houston, Robert Green and I designed the BabySeq Project to experimentally measure the medical, behavioral, and economic outcomes by prospectively sequencing both healthy and sick newborns and then following the consequences of returning results to them, their physicians and to their medical records.

AJHG: *What about this paper/project most excites you?*

Alan: Although thousands of both healthy and sick individuals have undergone genomic sequencing by now, BabySeq represents one of the first prospective, randomized controlled trials of sequencing for which disease detection was not a primary goal. By enrolling newborn participants regardless of their medical status we can achieve one of the less biased comparisons within a human population. Although our sample size is modest, we were surprised to find in the sequencing arm that 9.4% of the infants, including ten of 127 healthy newborns, harbored what we considered to be a monogenic disease risk alleles, in other words, genetic variants that are predicted to cause disease using current best practices for determining disease-gene association and variant interpretation. Such a high rate of predicted genetic morbidity suggests either that we currently underestimate genetic contributions to common disorders such as heart disease or cancer, or that our variant predictions of pathogenicity or assumed disease gene penetrances are over estimated.

I think the randomized controlled aspect of this study is something else that excites me. It is providing an important opportunity for Amy McGuire and her team at Baylor to more rigorously assess the psychological and social implications of having genomic information at an early age. Funding permitting, we aim to follow the BabySeq families in both the sequenced and control arms well beyond the one-year follow-up surveys currently in progress, and I expect that we will be able to provide some hard data to address some of the concerns surrounding potential negative implications of learning genetic information.

AJHG: *Thinking about the bigger picture, what implications do you see from this work for the larger human genetics community?*

Alan: This is a difficult question to answer! Of course, just about everyone who has interviewed me has asked whether I think sequencing of newborns will become standard of care. The first point I make is that, for the foreseeable future at least, we absolutely do not view this as a replacement for traditional newborn screening, which targets a carefully chosen group of treatable diseases using tests with well-established and high degrees of sensitivity and specificity.

There is no question in my mind that rapid genomic testing is indicated for newborns with undiagnosed medical conditions that may have a genetic basis, and it is gratifying to see that geneticists and neonatologists are rapidly adopting this, and that third part payers are finally starting to come around and reimburse for this. Although I'm confident the data will eventually show that the risks of newborn sequencing in healthy infants are acceptably low, the benefits will be harder to establish and are likely to be uneven: most newborns will not have immediately actionable findings, but identification of carrier states will occasionally lead to identification of couples at-risk for future pregnancies, and presymptomatic diagnosis of even untreatable conditions such as Duchene muscular dystrophy, will help some families avoid having affected children in the future. Occasionally, and with increasing frequency, an early diagnostic finding will lead to potentially life saving interventions or surveillance, as in the case of the families we identified with variants for hereditary cancer syndromes. As our understanding of disease-gene associations and variant interpretation improves, more and more children will stand to benefit from such information.

The newborn period is a hectic and disruptive time for new families, so I think genomic sequencing for healthy babies is more likely to be eventually offered in late infancy or early childhood, much like many vaccinations are offered today. Before this happens though, it will be up to us, the professional genetics community, to engage with our colleagues, legislators, third party payers, and most importantly the public, in a discussion to determine when the broader societal benefits justify the risk and the costs, and to ensure that genetic information is protected to avoid misuse and discrimination.

AJHG: *What advice do you have for trainees/young scientists?*

Alan: Follow your heart and pursue the questions that excite you, but be mentally flexible and look for opportunities to work with outstanding scientists who will appreciate and support your efforts. Early in my postdoctoral career, my advisor passed away suddenly and I was faced with a career-altering dilemma. I was fortunate to find an outstanding new mentor in Dr. Lou Kunkel, and my career path shifted abruptly to focus on neuromuscular disease, and eventually genetics and genomics of rare diseases. Science, and society, are constantly evolving, so put aside your preconceived notions of what "should" or "will" happen, and follow the data and opportunities wherever they lead.

AJHG: *And for fun, tell us something about your life outside of the lab.*

Alan: I like learning about new things, so I tend to be a generalist with broad interests who enjoys tinkering and trying different things. I'm not an expert in any one area, but I've dabbled in woodworking, I like repairing broken things, from dishwashers to lawnmowers (YouTube is great for that!), and I've got a killer fish tank at home. I also love to be outdoors, and I'm just as happy raking leaves, cleaning my gutters, or shoveling snow in the middle of the night as I am kayaking or skiing.

A longtime ASHG member, Alan Beggs, PhD, is Director of The Manton Center for Orphan Disease Research at Boston Children's Hospital and the Sir Edwin and Lady Manton Professor of Pediatrics at Harvard Medical School.

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