Lifeline

For more on **next generation sequencing** see **Review** page 492

Rufus Olusola Akinyemi is a physician–scientist working as a senior research fellow at the Institute for Advanced Medical Research and Training, College of Medicine, University of Ibadan; and a consultant neurologist to the University College Hospital, Ibadan, Nigeria. He uses the research tools of genomics, cellular and molecular biology, epidemiology, biobanking, and implementation science to tackle vascular and degenerative brain disorders and promote brain health, particularly in people of African ancestry.

What have been the greatest achievements of your career?
Charting new paths in brain research in Africa through work in vascular cognitive impairment, conducting the largest study of stroke in Africa with novel discoveries of genetic risk variants, and pioneering neurobiobanking in Africa.

What inspires you?
I'm inspired by the need to find sustainable solutions to the multiple challenges to achieving optimal brain health in people of African ancestry.

What do you think is the most neglected field of science or medicine at the moment?
The nexus of inequity, genes, environment, behaviour, and health of global populations.

If you had not entered your current profession, what would you have liked to do?
Core public health.

Who were your most influential teachers, and why?
Professor Adesola Ogunniyi (Ibadan, Nigeria) and Professor Rajesh Kalaria (Newcastle, UK) have been most influential in shaping my development as a physician–scientist with a bench-to-bedside research framework. They believe in me and have together encouraged me all the way.

If you wrote an autobiography, what would be the title?
Pillars of progress: lessons from adventures in brain science.

How would you improve the public's understanding of research?
By entrenching robust public engagement within every research plan.

What was your first experiment as a child?
I enjoyed gazing at and counting stars in the sky.

What one discovery or invention would most improve your life?
Unravelling how and why we age and accumulate deficits, and finding a permanent cure for ageing.

What is the best piece of advice you have received?
From my Dad while in high school: "Remember the son of whom you are".

Focal Point

Next generation sequencing in clinical diagnosis

Next-generation sequencing (NGS) was developed more than a decade ago to facilitate sequencing of large amounts of genomic data. Use of NGS in clinical diagnosis is now widely accepted, with varying roles from gene panel or targeted sequencing, through whole exome sequencing (also termed clinical exome sequencing), to whole genome sequencing. NGS was first applied to clinical diagnosis when clinical exome sequencing was launched in 2012. The neurology community, although recognising its technical limitations, including non-uniform coverage and the difficulty in sequencing or analysing certain genomic regions and lack of ease in detecting certain types of variants, still believed the new technology had benefits to offer. The first scientific reports showed that clinical exome sequencing was able not only to successfully identify both rare and common single nucleotide variants and small insertions and deletions across coding exons and flanking splice sites of genes, but also to achieve a higher diagnostic rate than most of the traditional molecular tests, such as single gene sequencing, small gene panels, or chromosomal microarrays for rare Mendelian disorders.[1,2] Furthermore, diagnostic rates between laboratories were surprisingly consistent despite differences in the capture kits used, bioinformatics pipelines, and patient cohorts. Initially, variant confirmation was done with Sanger sequencing, which was, and still is in some estimations, considered the gold standard. However, laboratories soon began to develop internal quality measurements to determine the necessity of confirmation for each variant.[3] We now know that there are genomic regions, and conditions in which variant abundance is relevant to disease, for which NGS is a better method than Sanger sequencing, raising the question of whether Sanger sequencing should be replaced as the gold standard.[4]

Hane Lee, Julian A Martinez-Agosto, Jessica Rexach, Brent L Fogel

1 Lee H, Deignan JL, Dorrani N, et al. Clinical exome sequencing for genetic identification of rare Mendelian disorders. *JAMA* 2014; **312:** 1880–87.
2 Clark MM, Stark Z, Farnaes L, et al. Meta-analysis of the diagnostic and clinical utility of genome and exome sequencing and chromosomal microarray in children with suspected genetic diseases. *NPJ Genom Med* 2018; **3:** 16.
3 Strom SP, Lee H, Das K, et al. Assessing the necessity of confirmatory testing for exome-sequencing results in a clinical molecular diagnostic laboratory. *Genet Med* 2014; **16:** 510–15.
4 Beck TF, Mullikin JC, NISC Comparative Sequencing Program, Biesecker LG. Systematic evaluation of Sanger validation of next-generation sequencing variants. *Clin Chem* 2016; **62:** 647–54.