

Fire Monkey High Molecular Weight (HMW)-DNA extraction

Helping to democratise DNA Sequencing and bring the benefits of genomics to low- and middle-income countries

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The rapid cost reduction of DNA sequencing over recent years is opening massive new markets for genomics and DNA sequencing. In the developed world, with technologies driving towards the \$100 human genome, new near-term applications range from bedside diagnostics for instant identification of antimicrobial resistant bacterial strains for tailored treatment, to sequencing all babies at birth, which will allow personalised medicine throughout a person's lifetime. In low and middle-income countries (LMICs), with less access to technology and lower budgets for healthcare, it is applications in planetary health that are likely to have the greatest benefit.

Planetary health is a new field and one that needs ideas and solutions that span multiple sectors and disciplines to guide the creative stewardship of our planet to protect our own health and that of the planet. Planetary health recognises that human health and the health of our planet are inextricably linked; and that our civilisation depends on human health, flourishing natural systems; and the wise stewardship of natural resources.

Human behavior is changing the climate, which is altering the pattern of diseases, mortality, human settlements, food, water; and sanitation for everyone. Known human impacts include flooding that can increase risks of water-related illnesses as well as vector-borne illnesses; and it has an impact on food production – both in terms of increased drought cycles, disease and diminished micronutrients in staple crops.

Infectious diseases – diagnostics and genomic epidemiology

One of the biggest applications of DNA sequencing for human health is in microbiology. Sequencing has a major role to play in identifying and monitoring the spread of infectious diseases, within and between the developing and developed world, between humans, animals and reservoirs in the environment. The human race is a monoculture which makes it vulnerable to the zoonotic disease threats that are increasing such as we saw with COVID, Ebola and Zika.

Genomic sequencing will eventually, completely replace traditional methods of bacterial identification and offers additional benefits of being able to accurately detect mutations and mobile genomic elements that can lead to zoonotic transfer, increased infectivity and drug resistance.

Sequencing pathogens is highly accurate and fast but has, until recently, been very expensive in consumables and facilities. COVID showed how knowing a gene sequence allowed a rapid vaccine development to an emerging pandemic; and ongoing sequencing enabled the tracking of COVID variants. All countries will build this essential capability in future.

The use of whole genome sequencing (WGS) in low to middle income countries has been predominantly through taking samples locally and then transporting them to out-of-country laboratories for specialist sequencing and analysis. RevoluGen technology incorporated into local laboratory workflows allows WGS to be carried out in country. For example, Fire Monkey is being used to look at the transmission of *Campylobacter* infections in Bangladesh. The Child Health Research Foundation, Bangladesh, supported by the Quadram Institute, UK have established a DNA extraction and sequencing facility in Dhaka under a grant from the Bill and Melinda Gates Foundation. The facility is also being used to sequence SARS-CoV2 genomes.

COVID sequencing capability has already been actively transferred into other LMICs under the COG-UK initiative, of which Quadram is a key member. Quadram has helped train specialist technicians in Zimbabwe, Fiji as well as Bangladesh in sequencing technology techniques for pathogen surveillance. As the sequencing price continues to fall, pathogen sequencing will become further democratised rather than be a rarity across all LMICs.

The Improved accuracy and information available from sequencing allows identification of antibiotic resistance genes and can have a direct impact on cost savings by avoiding the use of wrong antibiotics. The WHO is pushing for world surveillance in all countries of antibiotic resistance genes because they often emerge first in low-income countries.

Fire Monkey HMW-DNA extraction - advantages

RevoluGen's Fire Monkey high molecular weight (HMW)-DNA extraction offers a number of technological advantages that can support cost reduction and wider adoption of microbial DNA sequencing, growing existing and creating new markets:

- Fire Monkey sample preparation is easy to adopt and use as it is based on a familiar spin-column protocol that can be transferred to low tech laboratories without requiring major capital equipment investment or training. This ease of adoption with minimal changes to existing infrastructure makes it particularly suitable for LMIC use;
- Fire Monkey reagents are stable in conditions of high heat and humidity;
- Fire Monkey is the least laboratory disruptive technology of the few extraction technologies that can extract HMW-DNA;
- Fire Monkey produces HMW-DNA of the ideal length for long-read sequencing but can also be used for short-read sequencing surveillance. This flexibility facilitates hybrid assemblies as well as saves precious samples. It also means DNA can be extracted once from a clinical or environmental setting and the DNA stored for all sequencing needs (vs. culture and re-extraction);
- Fire Monkey comes in flexible versions from individual manual versions through to high volume automatable 96-well plate format. The measured introduction of the automated versions will drive adoption for high volume surveillance applications; and
- Fire Monkey simplifies the sample to result workflow supporting accessible multiplexed long reads with accessible HMW-DNA extractions for cost reduction.

The microbiology applications alone of HMW-DNA extraction of short-read, hybrid or long-read sequencing are going global and will become a multibillion-dollar market that will rise to prominence in the near future.

Population genomics – managing human disease

Non-communicable disease is rapidly emerging to become a major challenge for health care systems in LMICs. Cardiovascular disease, diabetes and cancer, are already becoming a leading cause of chronic illness and early death in LMICs.

As DNA sequencing costs reduce and today's innovative technologies become routine, new genomics markets beyond genomic epidemiology and microbial diagnostics will open up to LMICs. Cancer is a genetic disease where sequencing is already beginning to be used routinely for diagnosis and treatment selection. As poorer countries grow richer, cancer will eventually overtake infectious diseases as the main cause of morbidity and mortality as it already has in high income countries (HICs).

Large Bio banks of clinical samples have been collected and stored over a number of years. There is, however, a paucity of data and understanding of the genomic pre determinants of such diseases in many poorer populations. Area specific genomic databases are already starting to be developed across the whole world in order to describe the genetics of local populations.

Large population studies are already being recognised as important for many reasons. For example, in the middle east, there are plans for arranged marriages to potentially be screened for partner selection in order to reduce the cost of care for genetic consanguineous diseases.

Personalised medicine is clearly going to be based on an understanding of the genetic basis of disease in all populations. This will include the risks and opportunities for early detection and personalised intervention in different communities which are critical, and its use will accelerate over the coming years.

Obesity and related diseases such as atherosclerosis and diabetes are rapidly becoming a major problem in many previously poor countries as income levels rise. The genetics of the gut microbiome will play a large part in the management of these conditions now it is clear that starvation diets can cure many diabetics.

The use of generic medicines and in particular the opportunity afforded by low-cost simple practical approaches to whole genome sequencing will increase as LMICs grow in economic strength. The population genomics applications requiring HMW-DNA extraction for hybrid- or long-read sequencing offer massive growth opportunities in the medium term.

Rapid market growth opportunity

DNA extraction is a relatively small part of the total sequencing cost of a sample (extraction costs are on average between 0.2% - 2% of sequencing costs) but extraction numbers will increase in lock step with sequencing run numbers. Now even as the cost of each sequencing run continues to fall, all the independent market reports estimate that the global sequencing market will grow at a CAGR of between 17.5% to 19% until 2028. The sequencing market was worth somewhere between \$5bn and \$16bn in 2021 and is expected to reach between \$24bn and \$40bn by the end of this decade. This presents a rapid market growth potential in extraction and sequencing; and an opportunity that RevoluGen's Fire Monkey is very well placed to exploit.