# S*f*AM position statement: Whole Genome Sequencing in clinical microbiology

August 2016

The Society for Applied Microbiology (S*f*AM) supports people working in a range of fields where there are applications of Whole Genome Sequencing (WGS).

WGS is a tool that has attracted some controversy, with some seeing it as a panacea for identification and surveillance of pathogens, and others viewing it as a worrying trend that may leave microbiologists of the future lacking in basic skills of culture and identification. We do not seek to resolve this argument, but to lay out some of the areas where there is a clear purpose for WGS, either as a standalone solution, or as part of a suite of tools.

Strengths in the application of WGS exist in public health, epidemiology and clinical settings. As well as more efficient identification and genotyping, it is also possible to use WGS to stratify patients and target effective treatments. In surveillance of organisms and of antimicrobial resistance genes, WGS is likely to prove extremely valuable, in time.

It is important to note that the cost is currently prohibitive in some cases. A culture based method may be orders of magnitude cheaper, though it may also be slower and less precise. However, the cost of WGS is dropping significantly as the technology is adopted more widely and it evolves to become cheaper and easier to access and use.

Many laboratories are already using molecular methods, which have become more established over the past decade – a change that has served to introduce skills in this area that will be applicable to WGS as its usage increases.

Future clinical microbiologists will certainly need to learn WGS as well as traditional molecular and culture based techniques – it needs to be an add-on rather than a replacement in training. Additional skills in programming and bioinformatics would also be desirable.

Realistically, WGS is likely to come into public health and clinical settings as part of a mixed economy.

## Public health

The aim in public health is to **identify** a pathogen, **type** it, and **treat** patients and/or **prevent** further infections. In many cases, the information from traditional methods, including sequencing short pieces of the genome, is just as useful as that from WGS, but sometimes WGS is the most appropriate tool.

One example is in *Salmonella* serotyping and subtyping where traditional methods are very labour intensive and therefore expensive. WGS provides a more efficient and effective method to distinguish serotypes and subtypes within an outbreak,[i] as long as there is skill to interpret the information and bioinformatics tools to support that.

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WGS also speeds up drug resistance testing and can add greater information, particularly in cases where there are complex mixtures of low level resistance. It adds value to identification by eliminating the need to carry out many PCRs for each isolate. There is the potential to direct treatment, as well, if the genetic target of a drug is known – sometimes there are multiple targets, so using WGS is cheaper and more efficient than multiple PCRs.

## Epidemiology and surveillance

Clinicians want precise case definitions. With WGS we can see cases that are geographically distant but look very similar genetically, or that appear epidemiologically related but genetic analysis shows that they are unrelated. It can also be a powerful tool for surveillance of emerging infections, particularly in virology.

WGS contributes data that, when interrogated, can promote investigation of epidemiological links that might not have been obvious initially. The results of pathogen sequencing can lead to exploration of patient history that might not have been considered important.

The reverse can also be true – a group that looks at first to be epidemiologically linked might be a coincidence and WGS can provide the detailed information that looks at potential multiple exposures.

WGS can also identify mixed infections that might explain unusual epidemiological results from investigations that assume a single pathogen. It can also be powerful in distinguishing isolates that come from elsewhere in the world that might not be picked up based on local information and experience.

Much of the power of WGS in epidemiology is in being able to understand how several different types of data interact e.g. combining genomic predictions with reports of consumer behaviour.

## Phenotyping

WGS can complement classical phenotyping and also adds a lot more information. It's not just about typing; in time we will be able to predict with more and more certainty, from the genome, what the organism will be capable of doing. This has some particularly important applications in surveillance of antimicrobial resistance.

It will always remain the case, however, that organisms which possess the genes for a trait may not all be phenotypically similar and so WGS is unlikely to replace classical phenotyping entirely.

In some cases, the diversity is too great to be able to pick apart the data and form meaningful information about relationships between individual subtypes of a species.

There is also a danger that because WGS can work in so many cases, we lose the ability to culture pathogens and explore phenotype that way. There will still be cases where this is the best approach, even with wide adoption of WGS.

## Infrastructure and implementation

There is a significant investment required to establish WGS facilities. That said, there are now new, cheaper methods available, including real-time sequencing using the portable MinION kit.[ii]

In all cases, good systems for tracking samples through the entire process are vital. There are also advantages to centralising high performance computing infrastructure so all data is fed into a single point where analysis can begin.

It takes time to establish WGS in the context of a clinical laboratory. There is a huge pressure for bioinformatics to provide tools to interpret WGS data and integrate it with other data from more traditional tools and techniques.

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[i] Deng et al, J. Clin. Microbiol, January 2015, vol. 53 no. 1 212-218 "Comparative Analysis of Subtyping Methods against a Whole-Genome-Sequencing Standard for *Salmonella enterica* Serotype Enteritidis"

[ii] https://www2.nanoporetech.com/products-services/minion-mki