45 delegates from 31 organisations\(^1\) attended the workshop which provided a rare opportunity for such a diverse group to meet and to exchange their different perspectives. The workshop had delegates drawn from many relevant life science disciplines including pharma R&D, NGS quality monitors, CDx (companion diagnostics) developers and service providers, regulators and their Notified Bodies – along with other life science technology product and service providers. The purpose of the workshop was to consider the importance of NGS-based CDx to precision medicine, to consider the impact of the new EU IVDR on the industry and to identify some next steps that could optimise the timely delivery of safe and effective CDx.

**Introduction**

The development of sequencing technology has accelerated enormously. Sequencing costs are now below $1,000 per genome. It is now possible for just one sequencing machine to process up to 200 human genomes a day. The Wellcome Sanger Institute alone is capable of sequencing over 2 Petabases (10\(^{15}\)) of data (or ~20,000 human genome equivalents) per year.

There has been a rapid expansion in the number of large genome projects using hundreds of thousands, even millions, of genomes (see Nangle & Furness – *Drug Discovery World, Winter 2017-2018, pp 65-70*) Several market reports and scientific reviews have shown the rapid growth in the use of biomarkers and CDx in drug discovery and development. A recent report from Frost & Sullivan suggested these tools would be one of the key growth areas in the developing Precision Medicine market and could be worth $134 billion by 2025.

Historically, genomics had been the preserve of the discovery domains of the life science / biopharma R&D process, but now there were larger clinical genomics projects evolving, embracing medical diagnostics and clinical testing. The expansion of both areas required a greater need for scientists, clinicians and regulators to come together from these different sectors to address common issues, such as data reproducibility and standardization. Alignment of these standards would allow the potential of the same data sets and analyses to be used across both discovery and clinical research and development frameworks, such as using data analysed in research as part of CDx regulatory filings. In future we may be able retrospectively to rescue drugs in failed clinical trials if appropriate companion diagnostics could be identified which identify particular sub-populations that either positively or negatively respond to the drug. The growth of large genome and biobanking efforts also allowed the potential to stratify these populations to identify candidates for existing drugs, as well as candidate to participate in new drug trials with defined genotypes and/or phenotypes.

**The Bio-Pharmaceutical Industry perspective:** there has been a log-linear decline in the number of drugs produced per billion dollars invested since the 1950’s (*Scannell et al, NRD 2012, Hay et al, Nat Biotech 2014*). The current probability of success of a drug reaching market from initial research was around 3%. However, drugs with supporting genetic

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information have >2x increased chance of success over those without. Currently, approximately 50% of all marketed drugs have some genetic evidence supporting them. It is expected that 10% of all known drugs would have genetic predictors of efficacy. It was not unknown for pharmaceutical companies routinely to perform pharmacogenomic testing in development, but for many disease areas there can be challenges with statistical power due to insufficiently large populations in the data sets.

Genotyping by array costs around $65 per sample, whereas genotyping whole genomes is ~10x more expensive, but for some studies it is much more informative. So, it is important to use the right technology to address the question that is being asked. Whole genome data, while more expensive, provides additional data, such as the effects of non-coding sequence variation.

The UK Biobank is generating data on samples from 500,000 individuals, including a wide range of clinical and imaging data, and this generates over a trillion new data points a year. GSK, Regeneron and other companies are funding both exome and genome sequencing of these samples too. One example quoted showed that what had previously taken more than 18 months and over 1,000 emails to achieve, could now be achieved in 1 day using the UK Biobank data. The UK Biobank contains around 1,000 Loss of Function variants in genes which have the potential to predict likely actions of drugs targeting these genes. However, there are key issues around consent and the sharing of the results of genomic analyses with the contributing participants of the genomic data. UK Biobank has adopted the position that it would not share analysis results with the participants. Other groups are looking at mechanisms to share results, but there are still many ethical and legal issues, especially with the ever-increasing use of global clinical studies. Discussion during Q&A revealed that a CDx filing could in principle be for a particular analysis pipeline or tool for patient data. Furthermore, it was noted that evidence is emerging showing the utility of CDx for predicting oncology response.

The Genetics Testing Quality perspective: the EMQN (European Molecular Genetics Quality Network) was modelled on UK NEQAS and was launched in 1997 with EU FP4 funding. For EQA (External Quality Assessment), EMQN users register to participate and are provided with a biological sample, or samples (unknown to the user), which the user processes, analyses and then returns their results to EMQN. EMQN then compares the user’s results with their internal consensus-based standards and provide feedback to the user on both their own performance, and an anonymised summary of the results from all participants as graphs showing ranges and quartiles for each metric measured. There are currently no universal best practises guidelines for clinical implementation of NGS, and while participation is not compulsory, regulators and Notified Bodies do take note of EQA performance and if a lab is performing poorly can suspend testing activity. The EQA scheme for NGS has been designed to be platform-agnostic and can be run on samples from across different disease areas ranging from single genes to whole genomes.

In 2013, the pilot EQA had 24 labs participating, and by 2017 this had increased to 260 labs for germline testing and 100 labs for somatic testing. For germline testing, 70% of the data was generated on Illumina platforms, while for somatic testing, 40% was carried out on LifeTech platforms.

In 2017, 87% of the data submitted was mapped using BWA (Burroughs-Wheeler Alignment) and 64% used GATK (Genome Analysis ToolKit) for variant calling. User should be aware that both of these tools were originally developed for research purposes and have subsequently been adapted for clinical testing. For germline data, 92% of submissions achieved >80% sensitivity and 94% achieved >80% precision for GRCh37. For somatic data, 65% achieved >55% sensitivity and 94% achieved >80% precision for GRCh37. A paper summarising EQA findings up to 2016 is currently being drafted. While the test results were only shared with the lab being assessed, the summary data could be shared, and a list of participants is available, so a potential customer of a testing lab could find out if that testing lab has been
tested and could ask that provider to share their results. One of the test samples was a PGP (Personal Genome Project) individual and the consensus data obtained will be provided back to the PGP Consortium.

One key issue is the lack of a harmonised standard for the vcf (variant call format) files used to report variants, as it currently provides a framework format, but fields within it can be customised. EMQN were also looking how they might incorporate other analysis pipelines, including copy number analysis. Discussion reviewed how the EQA could be used to monitor or assess NGS processes. As the EMQN services could be applied to any NGS test lab, the EMQN could be used by any commercial instrument and/or kit manufacturers to ‘qualify’ their products. EQA systems are invaluable and it was recommended that manufacturers should collect this data. However, it was noted that while labs in the UK needed to take part in a quality process such as EQA (a mandatory requirement of ISO15189 accreditation), this was not the case in all countries.

**The Regulatory perspective:** the new EU IVDR entered into force on 26 May 2017 and transitional activities will occur until the date of application of the EU IVDR on 26 May 2022. By that point, existing CE-marked products will need to have been CE marked under the new framework. There are 3 key performance indicators that make up part of an IVD application:

(i) **Scientific Validity** – how good is the evidence for the association between the biomarker and the likelihood of response to the corresponding medicinal product?

(ii) **Analytical Performance** - how good is the IVD at detecting the biomarker?

(iii) **Clinical performance** - how good is the IVD at predicting which patients are likely to respond to the corresponding medicinal product?

Every IVD will require a new performance evaluation, but not all will require a new performance study. There are some basic requirements for all IVD performance studies and some additional requirements will apply to performance studies in different circumstances, for example, for surgically invasive samples, interventional studies, additional risks to subjects, studies that involve people from specific groups and companion diagnostics.

**CDx development**

The IVD regulations will embrace those devices used in clinical trials to stratify patients. One of the additional requirements will be to notify the competent authority and (unless using only left-over samples) the competent authority will then assess the application prior to the start of the study. The processes for the assessment of an IVD performance study can summarised as follows:

- Application -> Verification -> Assessment -> Plan trial -> Performance Study Reporting.
Discussion included the situation for rare diseases and other situations where samples may be very scarce. Although it was understood that there are currently no defined requirements for sample size, the sample size must be appropriate for the study to be undertaken taking into account the intended use of the device and performance requirements for the device. It was noted that the MHRA is working towards close alignment with the EU post-Brexit.

The Notified Body perspective: the first question anyone should ask themselves is, “Is it an IVD device or a testing service?” Most CDx will fall under [EU 2017-746](https://www.eur-lex.europa.eu) IVDR Annex VIII Rule 3 and be class C devices. These would require Notified Body certification. Notified Bodies were designated by an EU Competent Authority to perform conformity assessments. Assessment based on the evidence & conclusions provided, that the device conforms to the relevant requirements. As yet, no Notified Bodies are approved to perform conformity assessments under the new EU IVDR. Quality Management Systems (EU IVDR Annex IX) provide assurance that appropriate processes were in place to allow for CE certification. It was noted that CDx manufacturers should engage with the Notified Bodies as soon as possible!

![Diagram](https://example.com/diagram.png)

Once certified, there is an ongoing requirement on CDx for updates, including Incident Reporting, Post-market Surveillance Plans and Post-market Surveillance, Maintaining Clinical Evidence and Post-market Performance Follow-up (PMPF). For Class C & D devices, updates to the Summary of Safety and Performance are required to be submitted at least annually.

At least 3 months of QMS data are required before a CDx manufacturer should apply for assessment. Notified Bodies are not allowed to provide advice, but they are allowed to provide training. Some quality standards already exist, e.g.:

- Medical device QMS ([EN ISO 13485:2016](https://example.com/standard))
- Risk management for medical devices ([EN ISO 14971:2012](https://example.com/standard))
- In vitro diagnostic medical devices ([EN ISO 18113-1 to 4:2011](https://example.com/standard))
- Medical devices ([ISO 15223-1:2016](https://example.com/standard))
- In vitro diagnostic medical devices ([ISO 23640:2011](https://example.com/standard))

Several new quality standards are in preparation, including:

- Clinical laboratory testing and in vitro diagnostic test systems ([ISO /TC 212](https://example.com/standard))
• Sample prep from FFPE for molecular IVDs
• Multiplex molecular testing, and
• Clinical performance studies.

**The CDx Development and Services perspective:** Quality Management Systems are essential and analytical validation standards do not happen all at once!

Key activities can be broken down into Design Controls, Assay Development, Assay Software, Reagent and Control Manufacture and Regulatory Interaction. The intended use of an NGS-based assay should drive the selection of the assay platform and technology. It is the entire process (the “wet” and “dry” parts combined) that comprise the CDx and both laboratory and bioinformatics pipelines are the subject of regulatory scrutiny. There are some NGS Assay Validation Challenges and some initiatives have been set up to try and address these, such as the CDC’s Nex-stoCT Workgroup, set up to address gaps in metrics and processes for test validation and quality control, which has led to further Quality System standards such as the College of American Pathologist (CAP) All Common and Molecular Pathology Checklist, and the Wadsworth Center’s CLEP NGS guidelines which incorporate NGS specific requirements for both assay validation and laboratory performance. Quality assurance needs to be maintained and monitored throughout the pre-analytical, analytical and post-analytical phases of testing. For CDx, all the bioinformatics processes must be locked, validated and controlled.

In a recent FDA Fact Sheet on Tumour Profiling NGS, 3 levels of biomarker were defined: (i) Companion Diagnostics, (ii) Cancer Mutations with Evidence of Clinical Significance, and (iii) Cancer Mutations with Potential Clinical Significance. The High Complexity of NGS pipeline and the results generated causes challenges for:

- assay validation, requirements of assay performance needed to meet regulatory requirements as a Clinical Trial Assay (CTA) and then subsequently as a CDx
- Selection of suitable target capture approach and sequencing platform
- Bioinformatics challenges for analysis and reporting
- Revalidation of pipeline after upgrades/changes
- Long term storage and retrieval of data
Notes from the Afternoon Breakout Sessions

- AI/Cloud-based decision systems – are they medical devices?
- Could algorithms be medical devices?
- How could we ensure reproducibility? Use containerized bioinformatic tools and workflows?
- Regulator-approved/validated containerized pipelines?
- Medical device software does not need to be CE marked.
- A harmonized standard for all data formats is needed – FASTQ and BAM files are standardised, but the VCF file format allows flexibility in the contents included. There should be consensus-driven effort including industry input/feedback.
- How might one establish performance standards for VCF files?
- Standards are required for data, reference genomes, reference materials and QMS.
- There need to be enhanced clarity around definitions – e.g., was a genome sequence 1 analyte, or 3 billion analytes?
- CDx deployment in clinical trials is variable in different regions.
- Different information is required for CE mark in the EU and the IDE (Integrated Development Environment) in the USA.
- Alignment between pharma companies - patient receiving the test differently across the world.
- Standards – national vs international? Mandatory vs optional?
- Versioning and provenance of data sources.
- FDA is looking for industry assistance to co-develop standards.
- There is significant alignment of standards across EU countries now, and introduction of the new IVDR regulations should streamline that process.
- Can an algorithm be a medical device? Currently IEC 62304:2006 is a standard for implementation of software.
- For genetic testing, could one have a software-only IVD? Currently there were no software-only IVD applications. Anyone interested should begin a dialogue ASAP with a Notified Body.
- Most tests to date have been developed under the health institution exemption, with the exception of NIPT (Non-Invasive Prenatal Testing).
- Illumina had CE-certified their complete wet/dry process, but others had just CE marked the dry lab component.
- How many bioinformatics developers were working in stakeholder organisations (e.g., Notified Bodies, Industry, Patients)?
- Is there potential for the MHRA and EQA to ‘link up’ to approve containerised software solutions to provide modular tools in a pre-approved format for end users?
- Can the reference material from EMQN/NIBSC be generated with a common specification? Such an approach would be useful where possible but could not be done for everything.
- How might one convert great public research bioinformatics tools into regulatory-compliant tools (e.g. GxP) for CE marking? Was there a way to get public development tools under a controlled environment?
- Interested parties should engage with the Technical Working Groups responsible for writing standards by engaging with their Trade Organisations (BIVDA in the UK and MedTech Europe more broadly) who have a standing invitation to take part.
Conclusions:
The workshop provided a great forum to share knowledge across all the domains within drug discovery and development, and in particular, the application of genomics and bioinformatics to these processes. It also helped to identify some gaps in knowledge and expertise across domains which provide future opportunities for education and training, such as:

- a non-partisan overview of the rapidly changing NGS technologies,
- new developments in bioinformatics (such as containerized software solutions), and
- the roles of quality assessment, regulators and notified bodies in helping users to implement these technologies in the real world.

In addition, some more specific areas were identified where a non-partisan body such as the Pistoia Alliance could facilitate bringing together a range of interested parties, for example:

- to define standards for data, reference genomes, reference materials and QMS,
- to define some standards for data formats (e.g., VCF for regulatory applications),
- to define ways to standardize processes (e.g., containerised tools or workflows) for regulatory applications,
- identifying commonality and differences between research and clinical data analysis standards, with the goal of aligning them as much as possible with minimal increased effort.

A need was also identified for more discussion around how changes to these processes may impact ethical issues, such as changes to consent and/or data sharing.