Category

Best Startup

Product/Solution Name

SeqOne | IntensiveGene

Date of Approval

N/A

Indications

Patients in Intensive Care Units (ICUs).

Therapeutic Categories

Proof of Concept (POC) focusses on Nephrology in ICUs, but long term objectives is to have solutions covering most frequient medical indications in ICUs as well as pharmacogenomics.

Background information and need for solution/product

Intensive Care Units (ICUs) are a vital part of our healthcare system, treating an estimated 50M patients per year. ICUs account for a disproportionately high share of healthcare costs with a recent study in the US estimating that they represent 13.3% of hospital costs, 4.1% of the US national health budget and 0.72% of GDP.

Integrating genomic medicine into Intensive Care Units (ICUs) is not only crucial but also holds immense potential to significantly improve patient outcomes while reducing healthcare costs. By harnessing the power of genetic testing, ICUs can expedite diagnoses, optimize therapeutic options, minimize unnecessary procedures, and effectively manage limited ICU bed resources.

However, to realize this vision, it is imperative to address the technical obstacles hindering the adoption of genomic medicine in ICUs:
-> With an estimated 20% of ICU admissions suffering from an illness that could be genetic in origin, genetic testing could speed diagnosis, help find the best therapeutic options, prevent unnecessary procedures, and ultimately free up limited ICU beds. Pediatric patients are unable to communicate clinically relevant information that could orient the medical team making genomic medicine even more important for this group. The BabySeq project, a recent study involving genomic information from 157 newborns. suggested that “over 10 percent of infants may carry unanticipated monogenic risks for actionable conditions that over [three to five] years will result in important medical consequences for those infants and their families". This number could be expected to be higher in the context of the ICU.

-> Because of the time pressures medical teams face in prescribing therapies, there is a higher incidence of adverse drug reactions in ICUs. A study in the UK estimated that Adverse Drug reactions in ICUs affected over 18% of patients and resulted in avoidable costs of £2B per year, numbers that could be mitigated through the use of pharmaco-genomics to better predict patient reactions to drugs prescribed in the ICU.

The broader use of genomics in ICUs could revolutionize practice, significantly improving patient outcomes while enabling significant savings to one of the costliest components of our healthcare systems. However, for this vision to be realized, technical obstacles that are slowing the adoption of genomic medicine in ICUs must be addressed. SeqOne | IntensiveGene is a solution designed specifically to facilitate genomic testing in ICUs to improve ICU patient outcomes while reducing costs.

History of the development of the solution/product

The drive to create SeqOne | IntensiveGene stemmed from discussions with medical professionals responsible for the treatment of patients in Intensive Care Units. They unanimously stated that having access to faster more accurate genomic analyses could significantly improve patient outcomes by speeding time-to-diagnosis, eliminating incorrect diagnostic hypotheses, and enabling better selection and dosing of prescribed therapies..

Based on this input, we set out to revolutionize the turnaround times for genomic tests in ICU environments. Through our proof-of-concept deployed accross multiple hospitals, we achieved a remarkable 75% reduction in turnaround times, delivering documented positive clinical results. These achievements were further validated through the presentation of our first POC results at a prestigious conference in New York in November 2022."

Current turnaround times for routine genomic tests are far too long to be of use given the compressed time scales in ICUs. Generally, these turnaround time for NGS genomic tests can range from a few weeks to a couple of months. This duration includes sample preparation, sequencing, data analysis, and result interpretation. It's worth noting that more complex tests, or those involving extensive data analysis may require longer turnaround times.

It became apparent that in the ICU environments, considerably shorter turnaround times would be necessary:
-> Ultra-fast* (Less than 2 days) – primarily used for critically ill patients at the time of admission
-> Fast (Less than a week) – for diagnosing and validating therapies once a patient was stabilised

*It should be noted that while turnaround times below 8 hours have been achieved in specially controlled environments with expensive equipment and significant numbers of qualified staff on-hand, such performances are unattainable in normal routine environments at a reasonable price.

Summarising the requirements we aimed to address, we identified five key criteria:
-> Significantly faster turnaround times
-> Ease of deployment in labs
-> Affordability
-> Ability to provide medically actionable inputs to key medical decisions,
-> Deployable in labs with limited resources to ensure equality of access to these lifesaving technologies.

SeqOne's objective was thus to develop an end-to-end solution that met these requirements to provide ICUs with a cost-effective and easily deployable solution. We therefore opted for three key technological orientations:
1) We would build the solution on the clinically proven SeqOne genomic analysis platform that has

been in commercial use with healthcare providers for seven years, is clinically validated with CE-IVD certification, and has proved effective in clinical environments. The platform supports bioinformatic applications (called Worksets) that address unique medical questions (DNA analysis for rare disease, RNA analysis for cancer, HRD test for ovarian cancer, etc.).
2) We would develop vertical solutions to address specific medical indications as this would allow us to optimise each application to simplify interpretation of the raw data. These solutions would be packaged as “Worksets” on the SeqOne Genomics platform. We would rely heavily on machine learning to automate the process and hence shorten the time required to deliver medically actionable results without requiring large amounts of resources.
3) We would rely on a new generation of portable bedside sequencers that can perform sequencing close to the patient to minimize logistical delays. These sequencers produce “long-read” sequencing data that offers an additional benefit of detecting certain types of pathogenic mutations (variants in the language of healthcare) that are difficult or impossible to see using traditional sequencing technology.

Our plan was to launch a PoC (Proof of Concept) addressing the Nephrology area that leverage all of these innovations working in close collaboration with Pr. Mesnard, Senior Nephrologist, Head of Intensive care nephrology unit in Paris, France and Co-Director of the National center for TMA (CNR-MAT).

We deployed a proof of concept across several hospitals in France, successfully reducing turnaround times by 75% to the 3-4 day TaT target while delivering positive clinical results. The results of this first POC (Proof of Concept) were presented at a conference in New York in November of 2022.

We are now preparing to deploy our solution more broadly and are currently working on clinically certifying the Nephrology solution based on our POC. We will undertake a benchmarking of our solution versus a conventional approach to demonstrate the improved TaT, simplified deployment and operation as well as the improved clinical results. Armed with this information, our commercialization efforts will focus on the Nephrology community aided by our KOL relationships.

Longer term, our objective is to reduce turnaround times further through improved bioinformatics, better ML interpretation support and faster access to raw data by integrating data upload directly from the sequencer. We will also interpret the data from the sequencer “on-the-fly” meaning that we may identify relevant mutations earlier, further reducing TaT. Together, we expect these innovations to allow us to reduce TaT below 24 hours while maintaining or improving the accuracy of the results. In parallel, we plan to expand our coverage to other indications starting with pediatric heart disease and pharmacogenomics.

Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

SeqOne | IntensiveGene is a groundbreaking solution that transcends the limitations of traditional genomic testing in ICUs. Our innovative approach encompasses several key elements, including indication-specific applications, tight integration of analytics with the sequencer coupled with comprehensive machine learning approaches based on innovative long-read bioinformatics.

These innovations enable us to provide fast, relevant molecular insights to any ICU, irrespective of resources or expertise. By significantly reducing turnaround times, automating diagnosis through

machine learning, and continuously updating our solutio to provide medical teams with the latest, fast evolving genomic knowledge, we are empowering ICUs to prevent adverse drug reactions, expedite diagnosis and therapeutic decision-making, and revolutionize pediatric care in ICUs

SeqOne's objective with the SeqOne | IntensiveGene solution is not to create a prototype that only works in ideal conditions with huge amounts of dedicated resources, but something that can be used by any ICU to deliver fast, relevant molecular insights. For this reason, we have focused on the deployability, cost, and human resource requirements of the solution.

We quickly realised that to achieve our goal we needed to take a holistic approach which involved examining each step in the genomic testing process from sample preparation to the generation of the final clinical report.

Key innovations
1) Indication-specific applications: As mentioned earlier, one of the challenges in reducing turnaround time in genomic tests in ICU environments is the diversity of indications, each with its own symptoms, that must be addressed. This is especially challenging as the interpretation of the data needs to be performed in an environment where geneticists with expertise in the specific illness of the patient are not always on-hand. This area has been one of the areas of SeqOne's research focusing on the following:

a. Creation of vertical "applications" each optimised for a specific medical indication. Verticalizing in this way has made it easier to optimise the whole process for the patient's indication, thus making it easier to obtain results. We call these vertical appliations "Worksets".
b. Machine Learning-driven variant prioritisation (the identification of pathogenic mutations) based on clinical information. To this end, we have developed a technology called Phenogenius that prioritises mutations based on symptoms (phenotypes in the medical lexicon) to help automate diagnosis. This automation of the interpretation of patient data reduces turnaround time and diagnostic errors.
c. Providing real-time updates to diagnostics. Thanks to the growing volume of research in genomics, there are approximately 100 new pathogenic mutations that are discovered each day. It is thus important to update medical teams on new discoveries that could impact the patient's diagnosis and therapeutic strategy. To address this, SeqOne has developed a system called GenomeAlert! that continually monitors the fast-evolving genomic knowledge and notifies the medical team about any recent findings that could impact one of their patients.

2) Bedside sequencing: We decided to build our solution around a portable sequencer that could be deployed at the patient's bedside while sequencing in "long-reads" that enable the identification of certain mutations undetectable using conventional methods. The sequencer in question is not currently clinically certified, meaning that initial deployments are done as proof of concept in research environments. However, we expect the sequencer in question to be certified in the near future opening the door to large-scale clinical deployments. This sequencer was chosen because it offered several benefits; i) Since it could be deployed at the bedside, it reduced logistical delays, ii) The sequencer could analyse a single patient at a time meaning that there was no delay waiting for enough patient samples to "fill up" one of the larger sequencers. iii) The chosen sequencer enabled "long-read" sequencing that reveals certain important types of mutations that are difficult to identify using traditional sequencing technology, and iv) The sequencer offers performance and cost benefits that would allow us to hit our targets.

3) Tight integration of sequencer and bioinformatics including sequencer-level support for data transfer. This integration requires tight collaboration between the sequencer manufacturer and SeqOne in order to ensure clinical grade security and traceability while ensuring fast and seamless data transfers.

4) Long-read bioinformatics: As mentioned previously the sequencer enables long-read sequencing that can identify certain types of genomic alterations virtually undetectable using conventional sequencing while having a high degree of medical relevance. SeqOne has developed specific bioinformatic approaches, working in collaboration with the sequencer vendor in order to optimize mutation detection using this new type of data. These analyses involve machine-learning-based noise reduction and variant identification to improve accuracy in variant identification.

We chose to evaluate our POC in the area of nephrology with a KOL from the Parisian Hospital network (APHP) who is Senior Nephrologist, Head of Intensive care nephrology unit in Paris, France and the Co-Director of the French National Center for Thrombotic MicroAngiopathies (CNR-MAT). During this PoC were able to confirm our ability to reduce TAT to under 4 days in clinical routine conditions while demonstrating our solution's capacity to detect important mutations, such as the CFH:CFHR1 hybrid gene, that were not easily detectable using traditional approaches.

Two brief examples of why speed matters:
>Patient 1: 57 years old man, HTA, kidney disease (November 2022). Admitted to the ICU for pulmonary hypertension, dyspnea. Alteration of mental status, TMA, and Hyperhomocysteinemia were observed leading to clinical suspicion of methylmalonic acidemia. Molecular diagnosis of MMACHC pathological missense variant was made too late to prescribe treatment with eculizumab, Extracorporeal membrane oxygenation (ECMO) that would have saved his life. The patient died despite the existence of lifesaving treatment.

> Patient 2: 34-year-old man with malignant hypertension (April 2022). The patient suffered from hypertension from the age of 18. He suffered an acute kidney injury with anuria and malignant hypertension with a stroke in April 2022. Renal biopsy revealed the absence of glomerular TMA and severe vascular lesions. Fast molecular diagnosis revealed: CFH pathological missense variant leading to the prescription of vitamin B12 and eculizumab leading to patient recovery.

How SeqOne | IntensiveGene will improve the human condition
The use of genomics in ICU has the potential to deliver several key benefits:
1) Pharmacogenomics for the prevention of Adverse Drug Reactions (ADR): By their very nature, ICUs are places where patients, often weakened by serious health conditions, are prescribed a large number of potent drugs. It is not surprising therefore that studies have shown that at least 17% of ICU patients suffer from ADRs, a number that many studies believe to be underreported. A recent study in the UK estimated that ADRs represented an avoidable cost of over £2B each year in the UK alone.
2) Accelerating diagnosis and therapeutic decision-making: Approximately 20% of patients in ICUs suffer from conditions that have symptoms that can be attributed to a genetic-linked disease. By performing genomic testing of patients from this population, genetic causes can be confirmed or eliminated greatly helping diagnostic decision-making.
3) Pediatrics in ICUs: Diagnosing very young patients is made even harder because of their inability to explain their symptoms aggravated by the fact that symptoms present differently or not at all in very

young patients. Genomic testing of the patient and relatives can help rapidly identify inherited and rare diseases greatly accelerating diagnosis and helping medical teams embark on the right therapeutic strategy far earlier than would normally be possible.

Implications for the future
We have clearly just scratched the surface in terms of reducing turnaround times in ICUs. Our future research will focus on the following areas:
-> Streaming bioinformatics: We will work to analyze the data generated by the sequencer as it is being produced rather than waiting for the sample to be completely sequenced. This means that pathogenic mutations could be identified more quickly reducing turnaround time.
-> Multiple applications to address specific types of ICU cases: We plan to extend the vertical application approach to cover an increasing number of therapeutic areas including cardio and orphan diseases.
-> ML advances to improve and further automate diagnostics based on clinical trials we plan to launch in each vertical.
-> Simplifying the capture of relevant clinical data by using LLMs (Large Language Models) to automatically extract relevant clinical information from the EPR (Electronic Patient Record) and other full-text patient infomation that may be available.

Each vertical application will be packaged as an application or “Workset” on the SeqOne genomic analysis platform.

More broadly, the fact that SeqOne provides a fully integrated platform for the deployment of ICU-targeted applications means that it constitutes the ideal platform for launching new ICU-specific genomic analysis apps. Development efforts and costs would be dramatically reduced because each app could leverage the SeqOne platform’s data integration, security, regulatory certification, etc.. The integrated, fast turnaround bedside sequencing that we are developing with our sequencing partners also opens the door to a more general availability of accurate, automated molecular diagnostics for use anywhere and be harnessed by medical teams "anywhere and anytime", a new usage that could transform the healthcare system as a whole.

Please provide appropriate references (ie Pubmed links)

Advantages of whole-exome/whole-genome sequencing in ICU
- https://pubmed.ncbi.nlm.nih.gov/31246743/
Advantages of whole-exome/whole-genome sequencing to manage kidney diseases patients
-https://pubmed.ncbi.nlm.nih.gov/30655312/

Fast ICU turnaround time proof of concept project in Nephrology
- https://www.youtube.com/watch?v=r8D4-m8SolE (presentation of fast TAT solution by Pr. Mesnard at Oxford Nanopore community meeting in New York 2022).
- https://www.igmpiindia.org/igmpiblog/newsletter.php?news=2848
- https://seqone.com/news/seqone-and-cnr-mat-pioneer-the-use-of-oxford-nanopore-to-improve-patient-outcomes-in-kidney-disease/

Automated variant prioritization including phentype-enhanced ML-driven prioritization
- https://scholar.google.com/citations?view_op=view_citation&hl=en&user=b5MFtHIAAAAJ&cstart=20&pagesize=80&citation_for_view=b5MFtHIAAAAJ:GnPB-g6toBAC

- https://scholar.google.com/citations?view_op=view_citation&hl=en&user=b5MFtHIAAAAJ&cstart=20&pagesize=80&citation_for_view=b5MFtHIAAAAJ:GnPB-g6toBAC
-https://scholar.google.com/citations?view_op=view_citation&hl=en&user=b5MFtHIAAAAJ&citation_for_view=b5MFtHIAAAAJ:ns9cj8rnVeAC
- https://www.medrxiv.org/content/10.1101/2022.07.29.22278181v3
- https://phenogenius.streamlit.app (open source version of Phenogenius co-developed with University of Grenoble)

Dynamic monitoring and alerts based on evolving research discoveries in genomic medicine
- https://www.medrxiv.org/content/10.1101/2021.07.13.21260422v1