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Messages from the third International Conference on Clinical Metagenomics (ICCMg3)

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Abstract

Clinical metagenomics (CMg), referring to as the application of metagenomic sequencing of clinical samples in order to recover clinically-relevant information, has been rapidly evolving these last years. Following this trend, we held the third International Conference on Clinical Metagenomics (ICCMg3) in Geneva in October 2018. During the two days of the conference, several aspects of CMg were addressed, which we propose to summarize in the present manuscript. During this ICCMg3, we kept on following the progresses achieved worldwide on clinical metagenomics, but also this year in clinical genomics. Besides, the use of metagenomics in cancer diagnostic and management was addressed. Some new challenges have also been raised such as the way to report clinical (meta)genomics output to clinicians and the pivotal place of ethics in this expanding field.

Keywords: metagenomics; next-generation sequencing; microbiota; bioinformatics; conference report

1. Introduction

Clinical metagenomics, referred to as the application of next-generation sequencing to clinical samples in order to recover information of clinical relevance, is a fast-moving field standing at the intersection of clinics, microbiology and bioinformatics. On October 18 and 19, 2018, we held the third International Conference on Clinical Metagenomics (ICCMg3) at the Campus Biotech in Geneva, Switzerland. Nineteen talks (Table 1) were delivered to more than 150 people coming from 18 countries (Figure 1). The conference was divided into five main sessions. First we opened the conference by a bioinformatic session as we did for the previous conferences. Then we tackled the microbiota metagenomics aiming at developing personalized medicine. Lectures about clinical metagenomics as a diagnostic methods were delivered by speakers from various fields. We also held a session called “beyond clinical metagenomics” with talks about ethics and results reporting. Last, we went off the track with a session dedicated to clinical genomics, a field far closer to the routine diagnostic than metagenomics.

As for the previous reports published in *Microbes and Infection* [1,2], this yearly report aims at being a snapshot of where clinical metagenomics stands at the present time, what are the current challenges and the next envisioned steps. Last, most of the ICCMg3 presentations (as well as these from the previous ICCMg meetings) are available at www.clinicalmetagenomics.org in the archives section.

2. Implementing clinical metagenomics

Helena Seth-Smith stressed the importance of having the sequencing device in-house, in order to be familiar with all that comes with its environment, and also to reduce the time to results. She also pointed at the recent publication of the ESCMID Study Group for Genomic and Molecular Diagnostics (ESGMD) [3] tackling practical issues for the implementation of whole genome sequencing in routine laboratories.

Maria Asplund presented the results of a study focusing on the viral contamination of metagenomics sequencing of samples from human origin. Tracing back the contaminating sequences, she showed that 68% and 74% of the viral hits obtained from respectively reads and contigs were contaminating DNA from laboratory reagents that were subsequently identified as viruses by bioinformatic tools. Indeed, when mapped to a viral genome the coverage was very heterogeneous, unlike the true detection of viruses in samples where the genome coverage is homogeneous. She further stressed

that contaminants were detected in reagents in a stochastic fashion, adding some complexity to their identification in experiments. Her results underline the need for manual verification and expertise when it comes to the identification of microbial signatures in samples.

Liana Kafetzopoulou described her work on direct metagenomic sequencing with the MinION portable sequencing device (Oxford Nanopore Technologies, Oxford, UK). She used the sample preparation described earlier by the laboratory of Charles Chiu in San Francisco [4]. In order to detect RNA viruses in blood samples, the method uses a tagged random primer enabling a retrotranscription step followed by a PCR amplification of all the transcripts. Hence, enough cDNA can be obtained and sequenced by the MinION. As they were on the field in Nigeria, a Lassa fever outbreak occurred and her team started to sequence human samples in order to assess whether cases were linked (supporting a human-to-human transmission) or not, thus showing that portable sequencers can be of help at the onset of an outbreak in complement to conventional detection methods (e.g. RT-qPCR). Nonetheless, the field work came with several obstacles such as the heat and moisture, the power cuts and a sub-optimal access to the internet.

3. Our microbiota and personalized medicine

Eran Segal presented the results of many studies he conducted about the fine interplay between the intestinal microbiota and nutrition. Among the examples he gave, he showed that probiotics settle in a personalized fashion, some subjects being resistant to the colonization by probiotics [5]. After an alteration of the microbiota caused by antibiotics, probiotics may even delay the microbiota recovery (which is faster with autoFMT [6]). But the most illustrative results he showed about personalized medicine stemmed from the Personalized Nutrition Project. The post-prandial glycaemic response (i.e. the increase of glucose in the blood after a meal) was more connected to the microbiota of the subjects than to the food itself, paving the way for a microbiota-tailored diet. They indeed validated such an approach in an external cohort of 26 prediabetic patients [7] and results from a larger study (NCT03222791) are pending. Based on those results, he established a company named DayTwo that proposes a microbiota-adapted diet. The “algorithm diet” has now been tested on more than 2,000 subjects.

Bertrand Routy presented the role of some intestinal bacteria in response to immune-oncology (IO) treatments that have been a major breakthrough in anti-cancer therapies during the last decade (the

2018 medicine Nobel prize being attributed to its discoverers James Allison and Tasuku Honjo). Still, the efficacy of these new compounds remains variable. Along with the fact that antibiotics are a risk factor for treatment failure, B. Routy and colleagues found that good responders to IO treatments had an intestinal microbiota enriched with *Akkermansia muciniphila* and also a higher gene richness [8]. Accordingly, the intestinal microbiota of patients scheduled for IO treatment should be tested for their microbiota in order to assess the risks of failure, and possibly to restore the good bacteria using probiotics or other microbiota changes (TMF).

Jacques Ravel talked about the vaginal microbiota, which has not been as under the spotlights as the intestinal one has been. From his former work [9], J. Ravel and colleagues showed that healthy American women could be clustered into five groups according to their vaginal microbiota composition, with four out of five being outrageously dominated by a specific *Lactobacillus* species. The fifth group showed more diversity and was more frequent in African and Hispano – American women. This group was associated to a higher risk of pre-term birth, but not in African-American women, supporting that the risk factors of pre-term birth were not microbiota-related. He also showed that while women with dominant *Lactobacillus* species had a stable vaginal composition (except for periods time), those from the fifth cluster could experience some substantial variations, like a dynamic dysbiosis.

In all, the microbiota speakers have presented various and compelling evidence that the microbiota will be increasingly considered in medicine for risk assessment and for modulation in case of deficiency for a specific function.

4. Clinical metagenomics: cell-free DNA sequencing

ICCMg3 welcomed two talks about cell-free DNA sequencing (cfDNA). Unlike conventional protocols bursting cells to access the nucleic acids, cfDNA sequencing focuses on the free “floating” DNA in samples. This could be relevant in situations like sepsis, where bacterial pathogens are destroyed by immune cells and their DNA released in the blood. Besides, cfDNA sequencing could bring less contaminants, especially in low-biomass samples. In a previous work, Silke Grumaz and colleagues had indeed observed that the bacterial DNA was more abundant in the blood of patients with sepsis than in those without [10]. In order to identify putative contaminants, she developed the SIQ score

based on the differential abundance of hits between the blood of patients with or without sepsis. The workflow is now being validated on larger cohort (Next GeneSiS trial [11]).

Next, Wei Gu showed some results about concomitant cfDNA in body fluids and plasma. While the pathogens present in the body fluids were also found in the plasma but at a lower abundance. He also showed some results about the comparison of cfDNA and 16S broad-range PCR. He reported that in two cases, 16S found a bacterium (*Streptococcus mitis*) while metagenomic sequencing found others (*Klebsiella pneumoniae*). Digital droplet PCR confirmed the presence of both. In a second case, 16S was negative while metagenomic sequencing retrieved a *Klebsiella* (formerly *Enterobacter*) *aerogenes* in a brain abscess. In human samples, especially those collected in the context of sepsis, the amount of human DNA is substantial. In the current clinical metagenomics pipeline though, the human DNA is discarded from the analysis. Interestingly, W. Gu showed that the copy number variation of human chromosomes could be measured by assessing the mapping rates of the reads on the human genome, thereby broadening the field of clinical metagenomics output.

Christophe Rodriguez shared his experience in implementing routine clinical metagenomics. He reported the results obtained from 29 patients suspected to be infected. He applied the MetaMIC (patented) workflow (considering both DNA and RNA) which results were discussed at a multidisciplinary staff (gathering microbiologists and infectious diseases physicians). He reported that in 25% cases, metagenomic sequencing brought some additional information compared to conventional testing. However a case of peritonitis caused by *Mycobacterium tuberculosis* was missed by CMg.

5. Clinical genomics

Not to set a precedent, we as a conference on metagenomics welcome five talks about genomics. Indeed, clinical genomics is a field far more mature than metagenomics and its integration in routine diagnostic is in the short-term, especially for tracking bacteria during outbreaks. John Rossen reported his experience of implementing the application of genomics in a routine microbiology laboratory, especially with respect to the ISO15189 certification. Such an implementation raises several questions: should the method be validated for all possible bacteria, what negative and positive controls should be used, how reproducible and repeatable is the method, what are the other methods to compare with, etc... In a European-scale ring trial [12], 20 strains of *Staphylococcus aureus* were

sent to five laboratories to be sequenced. Results were analysed at different levels, including cgMLST, and showed that the laboratories provided almost identical results. A similar ring trial with clinical samples is ongoing. Besides, in order to decrease the costs and turn-around-time of WGS during outbreaks, J. Rossen showed that from the genome of the epidemic strain, he could design a specific PCR aimed at identifying contact patients faster than WGS.

Willem van Schaik highlighted the diversity of bioinformatic tools that are available for clinical genomics and the difficulty to pick up one [13]. In terms of resources, he also pointed at the numerous antibiotic resistance databases and tools now available in order to search for antibiotic resistance genes in genomes: ResFinder [14], ARG-ANNOT [15], CARD [16], MEGARes [17], Deep-ARG [18] and ARGs-OAP [19].

The added value of WGS was challenged by Stephan Harbarth. Does WGS have an impact on the ongoing of an outbreak? Currently, the emergency during an outbreak is to implement containment measures such as dedicated wards and staff, cohorting and active surveillance (e.g. via molecular methods) of contact patients [20]. WGS could come after, in order to understand the dynamics and pathways of the outbreak. In this perspective, an exhaustive screening is required in order to obtain the highest resolution of the evolution of the strain causing the outbreak. As the relationship between strains is assessed via the detection of single nucleotide variants (SNVs), thresholds below which two strains are considered to be linked and above which two strains are considered to be distinct should be set. Nonetheless, setting such threshold is challenged by the inner evolutionary clock of the strain and likely to the local environment (e.g. exposure to antibiotics). Furthermore, long-term carriers can carry multiple populations differing by a few SNVs [21]. Given that only one strain is considered for WGS, the strain involved in the outbreak may differ from the one that was sequenced. Furthermore, mobile genetic elements carrying antibiotic resistance genes can move from a bacterial host to another host and thereby diversify the strains involved during an outbreak [22].

Tuberculosis is one of the deadliest human infectious diseases, with an estimation of one billion attributable deaths over the last two centuries [23]. WGS is becoming pivotal in the diagnostic of tuberculosis as it is a good substitute for antibiotic susceptibility prediction [24] and allows the analysis of the distribution of phylogroups around the world. Together with Georgian colleagues (Georgia being severely affected by the diffusion of multidrug and extremely – resistant [MDR and XDR, respectively] *Mycobacterium tuberculosis*) Sebastien Gagneux showed from the genomic analysis of

the MDR *M. tuberculosis* that prisons were a hot-spot for transmission, with an estimation that 40% of transmission events would occur between prisoners. In this perspective, Richard Neher provided some examples of online tools allowing a user-friendly analysis of the relationships between strains at the multinational scale, like NEXTstrain (<https://nextstrain.org/>). As WGS is getting closer to the routine laboratory for *M. tuberculosis*, designing a WGS report for clinicians was a challenge to tackle. Still in tuberculosis, M. Ticlla showed that the bacterial composition of sputa differed between Tanzanian patients suffering from tuberculosis and healthy controls. Moreover, the lung damage severity was also connected to the bacterial composition but not to the bacterial load of *M. tuberculosis*.

6. Beyond clinical metagenomics

Jennifer Gardy detailed the conception and design of a report for *M. tuberculosis* WGS analysis, using an iterative process of communications between the users (clinicians and non-clinicians) [25]. At the end, the report thought by bioinformaticians and microbiologists had little in common to that after consulting the users.

Finally, Beatrice de Montera raised several ethical questions related to the development of clinical metagenomics: should we investigate items that were not asked by the clinicians (e.g. finding an HIV virus in a sample obtained in the context of a bacterial infection)? Should we report this unwanted matter? How will we be dealing with the growing classification of subjects/patients according to their microbiome? Beyond the technical challenges raised by metagenomic sequencing, the ethical issues shall not be the easiest to address.

7. Perspectives

The presentations given during this third ICCMg showed that the field of clinical metagenomics is raising more questions than it actually resolves (Figure 2). From all around the world, clinicians, bioinformaticians and microbiologists are sequencing clinical samples obtained from a broad diversity of situations and they are finding more and more interesting findings, not only from the microbial side. How those findings will translate into medicine will certainly fuel the program of several further ICCMg. By the way, ICCMg4 will be organized next October 17-18, 2018 in Geneva.

Conflicts of interest

ER is consultant for Pathoquest. JS and ER received grants from bioMerieux.

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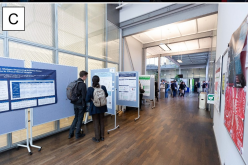
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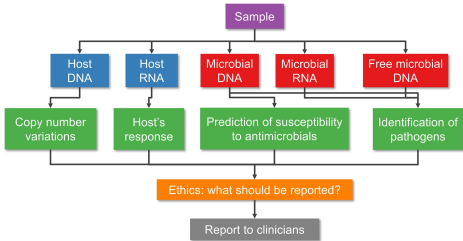
Figure 1: Pictures from the conference. A: The audience and Wei Gu delivering his talk. B: Networking during the coffee break. C: Interactions during the poster session. D: The ICCMg/SSM prize awarded to Ms Sarah Mollerup by J. Schrenzel and E. Ruppé.

Figure 2: Illustration of the growing complexity of the clinical metagenomics pipeline.

Table 1: Speakers and titles of the talks delivered at ICCMg3.

Table 2: Summary of the take-home messages and related key-points of the ICCMg3.





Session	Speaker	City (Country)	Talk
Bioinformatics	Helena Seth Smith	Basel (Switzerland)	A year in clinical bioinformatics
	Maria Asplund	Copenhagen (Denmark)	Extensive viral nucleic acid contamination in clinical samples
	Liana Kafetzopoulos	Salisbury (UK)	Nanopore sequencing: mobile metagenomics at the epicentre of a viral outbreak
Microbiota and personalized medicine	Eran Segal	Tel Aviv (Israel)	Personalizing treatments using microbiome and clinical data
	Bertrand Routy	Montreal (Canada)	Gut microbiota in immuno-oncology: from discovery to clinical trials
	Jacques Ravel	Baltimore (US)	Now moving to the vaginal microbiota and personalized medicine?
	Yan Shao	Hinxton (UK)	Caesarean section stunts the gut microbiota and predisposes pathogen colonisation during very early life
Clinical metagenomics	Silke Grumaz	Stuttgart (Germany)	Next-generation sequencing diagnostics of dehis
	Wei Gu	San Francisco (US)	Pathogen detection using cell-free DNA in body fluids
	Christophe Rodriguez	Créteil (France)	Metagenomic shotgun sequencing in the microbiology laboratory: routine implementation for complex cases
	Sarah Mollerup	Copenhagen (Denmark)	Investigation of viruses in human cancers by application of multiple pre-sequencing enrichment methods
	Monica Ticlla	Basel (Switzerland)	Diversity and composition of the microbiome in the lower respiratory tract is associated with lung damage in tuberculosis patients from Tanzania
Clinical genomics	John Rossen	Groningen (Netherlands)	Practical issues in implementing genomics in routine diagnostic microbiology
	Willem van Schaik	Birmingham (UK)	Challenges and opportunities for whole-genome sequencing-based surveillance of antibiotic resistance
	Richard Neher	Basel (Switzerland)	Real-time phylogenetic analysis of emerging pathogens
	Sébastien Gagneux	Basel (Switzerland)	Clinical genomics in tuberculosis
	Stephan Harbarth	Geneva (Switzerland)	How can WGS help in outbreaks? The point of view of the infection prevention and control
Beyond clinical metagenomics	Jennifer Gardy	Vancouver (Canada)	Lost in translation? Considering user needs in reporting clinical microbial genomics results.
	Beatrice de Montera	Lyon (France)	Symbiosis, an interdisciplinary concept with ethical applications

Message	Key points
The importance of contaminants in clinical metagenomics	Not only bacterial but also viral contaminants. Contaminants are detected in a stochastic fashion.
Personalized medicine	The intestinal microbiota can accurately predict the post-prandial glycemic response related to food intake. Intestinal bacteria such as <i>Akkermansia muciniphila</i> can potentiate the effects of immunotherapy used in cancer. The vaginal microbiota in increasingly showed to be associated with clinical conditions, especially when <i>Lactobacillus</i> are no the prominent species.
Portable clinical metagenomics	Can be useful for epidemiological aspects in complement to rapid diagnostic on the field.
Cell-free DNA	Cell-free DNA metagenomics sequencing is a promising alternative to conventional metagenomic sequencing, especially in sepsis.
Beyond clinical metagenomics	Reporting of clinical metagenomic results to clinicians is challenging and could get inspiration from genomic reports. Ethical issues: report the unwanted? Search for what was not asked to be sought?
Clinical genomics	Results from a ring trial showed that genomic analysis of <i>Staphylococcus aureus</i> was highly reproducible Added value of whole genome sequencing in outbreaks: assist the infection control unit in the understanding of transmission paths. At a national/international level, whole genome sequencing of <i>Mycobacterium tuberculosis</i> allows to identify hot-spots of transmission.