Revue d'anthropologie des connaissances

19-3 | 2025
Varia

ISO calling

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Electronic version
URL: https://journals.openedition.org/rac/38578
DOI: 10.4000/14k4b
ISSN: 1760-5393

This article is a translation of:
L'appel de l'ISO - URL : https://journals.openedition.org/rac/38445 [fr]

Publisher
Société d'Anthropologie des Connaissances

Provided by Bibliothèque cantonale et universitaire Lausanne

Electronic reference
Florian Jaton, "ISO calling", *Revue d'anthropologie des connaissances* [Online], 19-3 | 2025, Online since 28 August 2025, connection on 02 September 2025. URL: http://journals.openedition.org/rac/38578 ; DOI: https://doi.org/10.4000/14k4b

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Introduction

1 For at least thirty years, researchers in *Science & Technology Studies* (STS [1]) have described the central role of norms and standards in the construction and dissemination of scientific statements (Latour, 1987; O'Connel, 1993), technical artifacts (Mallard, 1998; Jaton, 2017) and biomedical procedures (Cambrosio *et al.*, 2006; Timmermans & Berg, 2003; Timmermans, 2015). By showing that reliability, accuracy and efficacy measures depend on long and costly stabilized (and stabilizing) referential networks, these inquiries have succeeded in depicting technoscientific and biomedical knowledge as at once constructed, objective, and performative (Busch, 2013; Callon *et al.*, 1999; Timmermans & Epstein, 2010).

2 This valuable line of research nevertheless suffers from a double blind spot. The first concerns bioinformatics sciences and technologies – now central to contemporary biomedicine (Chiapperino *et al.*, 2024) – which are supported by a host of standards and best practices whose constituent relationships have yet to be fully explored (Hà & Chow-White, 2021). The second concerns the numerous tests, inspections, audits and other standardization *trials*, as well as their preparation (Riom & Tanferri, 2024), which are an integral part of the ecology of technoscientific and biomedical practices, without, however, being the object of in-depth social studies.

3 By documenting part of the preparation for a bioinformatics pipeline standardization trial – more precisely, a national accreditation procedure aimed at guaranteeing the conformity of a software suite to an international quality standard (which itself opens up commercial opportunities) – this article aims to fill, in part, this double gap. Based on a four-month ethnographic study at a Swiss genomics center specializing in germline variant calling for clinical use, this article deepens our understanding of standardization in biomedicine – particularly in bioinformatics – by shedding light on both the tactical considerations involved and the interpretive flexibility such processes

entail. But also, on a more anthropological note, the text enriches the understanding of the social phenomenon of *preparation* in computational genomics, highlighting the situated production of a particular type of knowledge – at once epistemic, critical and strategic – aimed at making a bioinformatics platform meet an international quality standard.

4 The article is organized as follows. It begins by reviewing the importance of social studies of standardization processes, and stresses the need to combine them with studies of preparation and computer science in action. After a brief methodological detour, the article then delves into its field of inquiry to present the institutional, legal and technoscientific arrangements that shape and influence the actors' desire for accreditation. Finally, the article focuses on a decisive work meeting, where bioinformaticians prepare and equip their application for accreditation by comparing and discussing two software suites for variant calling for clinical decision support. The article concludes by discussing the new perspectives on the social study of standardization processes opened up by this analysis, highlighting the dynamics of negotiation, adaptation, and materialization of norms and standards in bioinformatics practices.

When social studies on standardization meet those on preparation (and on computer science in action)

5 Despite their seemingly "boring" nature (Lampland & Star, 2008: 11), standards – and, more broadly, standardization processes – have been the focus of quite a few publications in the social studies of science and technology. Historians of science were undoubtedly the first to tackle the topic, with the now-classic works of Robert Kohler (1994) on the collective shaping of the standard drosophila for genetic experimentation, Eviatar Zerubavel (1982) on the construction of the international time zone system, and Michel Foucault (1963; 1975) on disciplinary undertakings to normalize bodies and behaviors. Sociologists of science and technology, in the wake of Bruno Latour (1987: 116-160), then took up the issue, with major works by Joseph O'Connell (1993) and Alexandre Mallard (1998) on metrological practices in the technosciences. This empirical work – as well as some broader sociohistorical reflections undertaken notably by Alain Desrosières on statistical reasoning (2000) – has contributed substantially to more fundamental reflections on the role of standards in shaping the collective world, such as those proposed by Geoffrey Bowker and Susan Star (2000) on classification modes, Laurent Thévenot on regimes of engagement (2009), or Lawrence Busch (2013) for whom standards even become the recipes for reality.

6 But it is in the field of the social study of biomedicine that interest in standards has been – and remains – most pronounced, possibly for reasons of visibility. Indeed, as Stefan Timmermans and Steven Epstein (2010, p. 78) note, biomedicine is a field in which conflicts linked to the standardization of human beings are particularly acute, giving rise to numerous socio-technical controversies, themselves constituting privileged entry points for the social analysis (Rip, 1986). Hence a series of important investigations and propositions, notably by Alberto Cambrosio and Peter Keating (1992), and Monica Casper and Adele Clarke (1998), who showed that the tools and terminologies underpinning biomedical research and clinical practice are largely

shaped by institutional dynamics deeply embedded in power relations[2]. However, it is especially the work of Timmermans and his collaborators that has expanded and deepened the analysis of standardization processes in biomedicine. Their research has illuminated how protocols and standards are not only implemented but also reappropriated in various ways in practice (Timmermans & Berg, 1997; 2003), with particular attention to fields such as genomics (Timmermans, 2015). They have also shown how these standards can be repurposed as instruments of techno-political contestation (Timmermans & Almeling, 2009).

7 As interesting and important as they are, these socio-anthropological inquiries into standardization processes in biomedicine have some shortcomings, not least the almost total lack of consideration for applied bioinformatics. Although the work of Hallam Stevens has finely documented the structuration of this hybrid disciplinary field (2013) and the distinctive, increasingly naturalized modes of problematization that its practitioners contributed to disseminating in biomedical research (Stevens, 2016), little has been said so far about the processes of normalization and standardization that run through and shape bioinformatics. This omission is all the more unfortunate given that bioinformatics, and more broadly the mobilization of massive computational resources, plays a growing role in the representations and practices of healthcare professionals (Chiapperino *et al.*, 2024), while relying heavily – like applied computer science as a whole (Jaton, 2021a; 2021b) – on the dissemination and sharing of more or less arbitrary norms and standards (Hà & Chow-White, 2021).

8 A second shortcoming concerns the types of situations typically examined, which are most often embedded in routinized contexts. While a few socio-anthropological studies of standardization in biomedicine – such as Timmermans (1997) – have sought to closely document how actors engage with norms and standards in practice, very few have explored the situated practices that underpin the *transition* from non-standardized to standardized arrangements. In short, while we have substantial insights into standard (no to say standardized) practices, much less attention has been given to the specific mechanisms at play during *standardization trials*, such as tests, controls, and audits. These pivotal moments, with their often discretionary outcomes, can determine whether equivalences are established and whether networks can be expanded[3]. This may well represent a missing link in the social study of standardization, one that could also shed light on the subtle yet crucial distinctions, especially for those directly involved, between standardization, certification, and accreditation[4].

9 These elements in turn point to the question of *preparation*, which has recently received renewed attention within the anthropology of knowledge (Riom & Tanferri, 2024). Indeed, biomedical standardization trials cannot be improvised, given their highly regulated conditions for success and the significant financial, commercial, and institutional stakes involved. These trials therefore require *meticulous preparation*, the nature of which inevitably influences the fields of activity concerned. However, how and by what means this preparation is carried out remains poorly documented. In short, the skills, expertise and knowledge mobilized in *preparations for standardization trials* remain poorly understood, although they clearly have a significant impact on biomedical sectors seeking standardization.

10 It is precisely to help fill these gaps that the present article sets out to document the preparation for a standardization trial in a field affiliated to bioinformatics. Drawing on

the analytical genre of computer laboratory studies (Peerbaye & Vinck, 2023, pp. 53-54), this article aims to describe thoroughly some of the practices that contribute to this socio-technical phenomenon, as well as the institutional injunctions that set it in motion. And this implies the use of a specific investigation method, which I shall now present.

Method

11 This text is the result of an ethnographic investigation conducted between March and June 2022 at a Swiss center specializing in computational genomics. Drawing on the method proposed by Vinck *et al.* (2018) for investigating digital objects, as well as that proposed by Jaton (2019) and Jaton & Vinck (2023) for documenting the shaping of computational models, the ambition was to document some of the ordinary, concrete bioinformatics work that quietly underpins the development of so-called personalized medicine in Switzerland[5] (but also elsewhere).

12 The inquiry's primarily descriptive ambition was well received by the genomics center – which I'll call the Center from now on[6] – starting with the member of its steering committee in charge of bioinformatics affairs. This respected professional, active for many years in the field of benchmarking and standardization in computational genomics, was keen to show, and no doubt demonstrate, the necessity of a priori tedious standardization processes for the development of so-called personalized medicine. This support, if not for my research itself, at least for the topic of the *infra-ordinary* bioinformatics (Lefebvre, 2013), enabled me to gain privileged access to the Center. I was thus able to exchange freely with its staff and attend all their work sessions during the course of my investigation. However, for obvious security reasons, direct access to bioinformatics resources was forbidden.

13 Between the beginning of March and the end of June 2022, I was given access to the Center and a dedicated workspace. Like most bioinformaticians, I visited the Center on average twice a week, while the other days were devoted to tool maintenance, strategic thinking and coordination sessions (to which I was invited). This format of investigation enabled me to attend fifteen bioinformatics team sessions and eight coordination sessions. I also conducted around thirty interviews with all the Center's staff and observed four computer programming situations, using the method proposed by Jaton (2022).

14 Right from the start of my inquiry in March 2022, the question of the accreditation of the Center's bioinformatics platform was a major concern for its members – and consequently also for me. As we will explore in detail, this accreditation concerned the alignment of complex bioinformatics analyses with ISO 15189 – the International Organization for Standardization's norm[7] for quality requirements in medical laboratories. The process was both rigorous and demanding, requiring careful preparation for a costly official audit. A key component of this preparation was the production of a detailed report demonstrating strict adherence to the ISO 15189 standard, which served in turn as the basis for the audit itself.

15 This accreditation project, designed to attest compliance with a standard recognized by a reference authority, was of strategic importance to the Center, while posing numerous technoscientific challenges, particularly in terms of the speed, legibility, and

precision of genomic analyses. But another challenge, as we shall see, lay in the fact that the ISO 15189 standard governing the quality of biomedical laboratories was rather evasive when it came to quality criteria for computational and bioinformatics elements. The standard was not simply a recipe to be applied; it required the Center to design new quality control experiments, while developing appropriate interpretations of their results – a demanding, risky, and creative undertaking.

16 In retrospect, it seemed to me that a significant part of these concerns and difficulties were concentrated – not to say *folded* (Conley, 1998) – in a crucial working meeting held on the morning of March 28, 2022. It is this working meeting and the institutional elements weighing on it – which I subsequently had to patiently unravel – that the text proposes to meticulously describe, in order to draw out new elements on the practices of standardization in computational genomics and, more broadly, on the anthropological dynamics at play in preparatory processes within bioinformatics.

ISO 15189: A laboratory standard to govern them all

A complex institutional arrangement

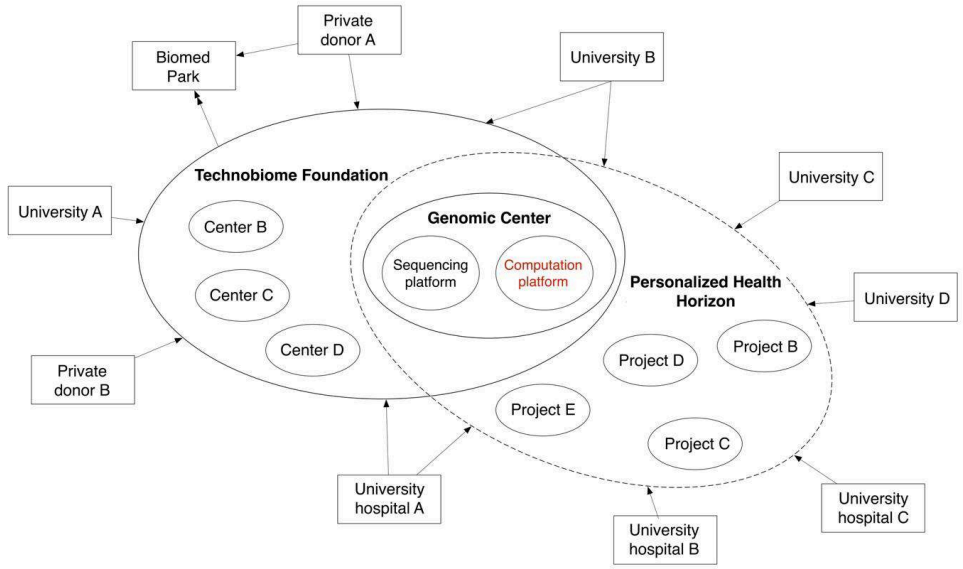
17 Many institutional factors feed the Center's strategy in its quest for accreditation. So let's start by drawing this thread together, by pointing out that the Center is made up of two platforms. A *computation* platform, whose members are responsible for what is commonly referred to as the "dry" part of genomic analysis, i.e. everything to do with the computer processing of sequenced data. The so-called "wet part", which encompasses biological sample preparation, amplification and sequencing, is handled by the *sequencing* platform, located three floors above the computation platform, within the same vast building dedicated to biomedical innovation, referred to here as the Biomed Park (see fig. 1). While the two platforms are closely linked, the seven members of the sequencing platform are, for the most part, biomedical laboratory technicians and scientists, while the seven members of the computation platform are, for the most part, data analysts, software engineers and IT security specialists, grouped together here under the broad designation of bioinformaticians.

Figure 1: Biomed Park entrance courtyard

Source: author

18 The Center, which thus brings together the sequencing and computation platforms within the Biomed Park, is the medical arm of a broader research and innovation initiative: the Personalized Health Horizon (referred to here as Horizon), launched in 2016. Administratively attached to a polytechnical school, this Horizon initiative aims to coordinate the many local projects in personalized health and precision medicine, under the guidance of a steering committee made up of professors, vice-rectors and hospital executives. Although the Horizon initiative plays a central role in the Center's strategic orientations, it does not have the legal means to directly hire salaried staff. This is why, from the outset, the Center has been administratively attached to the Technobiome Foundation (hereinafter referred to as the Foundation), a non-profit organization supported by private donors and academic institutions, and responsible for managing the groups housed within the Biomed Park (itself an organizationally autonomous structure, see fig. 2).

Figure 2: Schematic diagram of the institutional arrangement in which the Genomics Center operates. Solid arrows mean "financial support", double arrows mean "hosted by". The dotted circle around the Horizon initiative indicates its loose administrative situation



Source: author

19 Although the institutional arrangement that supports the Center may seem complex – and indeed is – this complexity does not necessarily imply a great deal of red tape, for as most of the heads of the various entities involved – Center, Horizon, Foundation, etc. – are the same people, who hold different mandates. Nevertheless, some administrative and legal obstacles remain difficult to overcome. For instance, although Horizon and the Foundation – the two umbrella organizations overseeing the Center – are supported by universities and university hospitals, this affiliation does not grant the Center formal academic status. As a result, neither the computational platform nor its "sister" sequencing platform is directly affiliated with a university or university hospital.

20 For the Center, being an institution with no direct academic affiliation has certain advantages, notably the flexibility to hire or restructure according to available financial resources. But it also has significant disadvantages, notably the obligation to present itself as a *service provider* to potential customers on whom the Center is heavily dependent. Indeed, even if the Center has benefited from substantial funding for its launch – notably to acquire high-end sequencing equipment and attract qualified personnel – the continuation and expansion of its sequencing and analysis activities depend, to a large extent, on the revenues it is able to generate. In this sense, even though it is part of a non-profit organization, the Center – and its two platforms – can be seen as a *semi-commercial entity* (Callon, 2021) seeking to generate income to reinvest in its parent organization, the Foundation. And it is precisely this need to generate revenue to ensure the sustainability of its activities – and, ideally, launch new projects and hire new collaborators – that fuels, at least in part, Center's desire to obtain national accreditation attesting to the reliability of its sequencing and analysis services.

21 But what does the accreditation of a medical analysis laboratory – whether active in genomics or not – mean for the case of Switzerland? And which institution is empowered to grant it? And on the basis of what criteria and trials? At this point of the

paper, it is important to briefly outline the status of medical analysis laboratories within the Swiss healthcare system.

Accreditation, you said?

22 The Swiss healthcare system is based on the obligation to subscribe to one of the many private insurances established in the country. The catalog of services reimbursed by these so-called "basic" compulsory insurances is governed by a law on health insurance, known as the LAMal, drawn up in 1999. Most of the standard services provided by a medical analysis laboratory in a clinical setting (for example, mycoplasma PCR testing) are therefore included in the LAMal catalog, and are covered (with deductibles) by the health insurance companies to which patients are legally obliged to subscribe.

23 As the main financial backers of medical analysis laboratories, private insurance companies have a say in the quality of laboratory services, which is assessed by a minimum *certification* called QUALAB[8]. Consequently, any medical analysis laboratory established in Switzerland – large or small – that offers services reimbursed by a health insurance company must be QUALAB certified, which means passing a series of internal and external quality controls every year.

24 While QUALAB certification enables effective quality control of biomedical analyses carried out under the jurisdiction of the LAMal, it remains a minimal quality label that does not involve systematic audits. And with the rise of next-generation sequencing – a sensitive, complex and heavily-equipped process – the Swiss Federal Assembly has passed a specific law requiring additional national *authorization* for any laboratory offering human genomic analyses (Federal Act on Human Genetic Testing, 2004). Under this law, any Swiss laboratory – large or small – wishing to carry out analyses of sequenced human tissue in a clinical context must undergo external quality control assessments in order to obtain authorization from the Federal Office of Public Health (FOPH). Only once this authorization has been granted by the FOPH can these medical laboratories have their genomic analyses covered by basic health insurance.

25 This Swiss federal law on genomic analysis also includes an article linking it to another federal law, passed in 1998, concerning medically assisted reproduction (Federal Act on Medically Assisted Reproduction, 1998). The article in question stipulates that laboratories carrying out genomic analyses in the context of medically-assisted reproduction must obtain national *accreditation* from the Swiss Accreditation Service (SAS), the body responsible for implementing the ISO 15189 quality standard for medical laboratories. This legislation thus introduces a *third and ultimate level of quality control* for medical analysis laboratories in Switzerland, structuring the system around three levels of control: a first, basic level, which covers analyses covered by QUALAB certification; a second, stricter level, which covers analyses requiring authorization from the FOPH; and finally a third, most rigorous (and costly) level, which applies specifically to genomic analyses, including – but not limited to – those carried out in the context of medically assisted reproduction..

26 At the time of this study, there were some sixty human genomics laboratories in Switzerland authorized by the FOPH, the vast majority of which were affiliated to major hospitals, most often university hospitals[9]. As a result, the vast majority of genomic analyses carried out in a clinical setting in Switzerland were performed by laboratories

affiliated to these same large hospitals, which thus found themselves in a quasi-oligopoly situation, often justified by the logic of geographical and institutional proximity[10]. For the Center, as a non-profit organization part of a larger foundation not directly affiliated to a university or hospital, entering this market of human genomic analysis was not an easy task, and attracting customers could only be done – at least from the point of view of its management committee – by *promoting its distinctive expertise*. In short, to gain a foothold in the small but promising market for clinical genomic analysis, the Center had to present itself as an exemplary genomics center, whose skills were attested to by a *superior quality label*. And it was to distinguish itself from other laboratories, attract customers, and gain financial independence (and also as a technoscientific challenge) that the Center decided to *accredit* its sequencing and analysis pipeline, in the wake of its launch in 2019.

27 The Center's accreditation project had two phases, the first of which concerned the "wet" activities of its sequencing platform, namely whole exome sequencing (WES), whole genome sequencing (WGS) and RNA sequencing (RNAseq)[11]. After completing the preliminary steps required by SAS – which led to the appointment of a quality manager and the engagement of a specialized subcontractor – the Center submitted its accreditation application in early 2020. In December 2020, an official audit took place at the Biomed Park, where SAS representatives meticulously assessed every step, from sample reception to the production of sequenced data in FASTQ format[12], based on the requirements described within the ISO 15189 standard. Despite a few minor "non-conformities", this standardization trial led to the official accreditation of the Center's sequencing platform, which was thus able to proudly display the prestigious "Swiss Accreditation" logo, attesting to its unique expertise (see fig. 3).

Figure 3: Official SAS logo attesting to successful accreditation

Source: www.sas.admin.ch

28 While the accreditation of the Center's "wet" part in 2020 was a success overall, it was only the first phase of a more ambitious project. The second phase of the Center's accreditation – in line with its desire to stand out in a Swiss clinical genomics analysis market dominated by laboratories affiliated to university hospitals – concerned its "dry" part, i.e. the computerized analysis of genomic data within the computation platform. Indeed, according to the Center's steering committee, extending SAS accreditation to include the computational pipeline was essential for positioning the Center as a provider of a fully integrated, high-quality service, from the sequencing of biological tissues to the delivery of analysis results in user-friendly formats such as Excel-like spreadsheets. This end-to-end offering was seen as the only truly compelling solution for clinicians seeking to quickly leverage genomic data to guide and support therapeutic decisions. In other words, extending SAS accreditation to the dry part of the Center – and thus to the work of the computation platform – was seen as the best way of making sequenced data truly *actionable* (Nelson *et al.*, 2013), i.e. capable of being mobilized rapidly, and with confidence, by clinicians in the *hic et nunc* of hospitals. And it was part of the uncertain extension of this accreditation – the centerpiece of an ambitious strategy for the development of precision medicine in Switzerland – that I set out to describe, between March and June 2022, in the recent but now established tradition of computer science laboratory studies.

A need for quick data actionability

29 Practical applications of sequencing and genomic data analysis are numerous, ranging from the genetic description of new animal species to human cancer immunotherapy (Jaton, 2023). For various reasons, including the existence of respected local private actors in the field of genomic analysis in oncology, the Center early on decided to focus on two specific areas: 1) Sars-Cov-2 genetic mutation monitoring (not discussed here) and 2) gremlin analysis, understood as the study of the genetic material passed on to offspring (typically from parents to children).

30 The Center's focus on germline analysis might seem curious, as the clinical, and thus semi-commercial, applications are not immediately obvious. Indeed, in Switzerland, for the genomic analysis of what is known as a "trio" (i.e., the biological father, mother, and offspring) to be covered by basic health insurance, there must be a compelling reason that only a clinical specialist, typically working for a university hospital, can confirm. Consequently, germline analyses tend to be conducted in laboratories that are authorized by the FOPH and that are thus most often affiliated with university hospitals (see section 3). So why has the Center focused a significant part of its semi-commercial strategy on germline analysis? Part of the answer lies in a new clinical trend that emerged around 2015, whose characteristics potentially suggest the use of services from a highly specialized external entity like the Center: rapid whole genome sequencing for neonatal intensive care units (rWGS for NICU).

31 The history of rWGS for NICU could be the topic of an entire paper, but let's focus on the essentials here. Launched around 2015, this approach is based on *rapid* whole genome sequencing in neonatal intensive care. A foundational study showed that this process, by providing a diagnosis in less than five days, could significantly reduce infant mortality (Willig *et al.*, 2015; Petrikin *et al.*, 2015). These results were confirmed in 2018 by a large clinical survey that demonstrated the impact of rWGS for NICU on

morbidity, mortality, and end-of-life care decisions (Farnaes *et al.*, 2018). Since then, several control studies (Kingsmore *et al.*, 2019; Clark *et al.*, 2019; Dimmock *et al.*, 2021) have refined these conclusions. Today, provided there is appropriate infrastructure, rWGS for NICU is recognized as a reliable and beneficial advancement in precision medicine, a reputation currently supported by the entire specialized literature (Owen *et al.*, 2022).

32 In 2020, the modest but real development of rWGS for NICU in the United States, Australia (Australian Genomics Health Alliance, 2020), and China (Wu *et al.*, 2021) is seen by the Center as an opportunity to pursue a noble cause, generate revenue, and highlight its expertise. Indeed, why not attempt to implement rWGS for NICU in Switzerland? This seems all the more relevant as the director of the computation platform – who is also part of of the Center's steering committee – has long-term working relationships with several clinicians at the largest children's hospital in Switzerland. This hospital, where newborns suspected of having genetic diseases are most often transferred and treated, thus appears as an ideal partner to initiate a collaboration.

33 As its name indicates, rWGS for NICU requires the *rapid* production of genomic analyses for patient trios. Furthermore, the Center's status as an external entity implies providing readable and directly usable results for the potential clinicians at this leading pediatric hospital. This is all the more crucial as the bioinformaticians of the computation platform cannot stay alongside the clinicians to interpret the results via command lines. As we will see, these complex requirements, combining speed and actionability (Nelson *et al.*, 2013), represent a major challenge for the accreditation of the computation platform's activities.

34 Regarding speed, determining the genomic variants of a patient from the DNA of their two parents is a complex process, requiring numerous non-trivial computational operations[13]. When the Center was created, the decision was made to adopt the open-source software suite GAT[14] for this step known as *variant calling*. Although this choice initially seemed appropriate – GATK is the gold standard for the analysis and interpretation of genomic data and is widely mastered by bioinformaticians – it quickly showed its limitations due to the dozens of hours required to perform the complex variant calling operations.

35 In 2020, to address the issue of GATK's slowness, which made it effectively unsuitable for use in rWGS for NICU, the Center's steering committee decided to acquire the proprietary software suite DRAGEN, along with its dedicated hardware, developed and maintained by the company Illumina[15]. This was a notable success, because once DRAGEN was installed and fine-tuned – which required many months of expert internal work – the duration of variant calling for a whole genome was reduced to just 45 minutes.

36 However, while the internal software components of GATK are widely known and accessible, this is not the case for DRAGEN. Unlike GATK, which is entirely open source, widely distributed, and extensively discussed, DRAGEN – despite its power and reputation – remains expensive and, for the most part, proprietary. This significantly limits its documentation, which is confined to the information provided by its distributor, Illumina. For the Center, this issue must be addressed head-on: in order to pursue its hope for rWGS for NICU as part of its desire for accreditation, it becomes crucial for the Center to better understand (and be accountable for) the relatively

opaque internal workings of DRAGEN as well as how it interacts with other components of the Center's pipeline.

37 A second issue related to the Center's desire for accreditation, connected to its hope for rWGS for NICU, concerns the actionability of the generated results. The variant call format (VCF) files produced by tools like DRAGEN or GATK tend to be quite technical and require advanced computational expertise to efficiently process and interpret. And by virtue of its more or less detailed knowledge of clinical settings, the Center's steering committee – and by extension, the computational platform – recognizes the importance of presenting results in a clear and concise manner. This means providing accurate yet simplified analyses that clinicians, who may not have extensive computational skills, can readily understand and use to inform their clinical decisions. Consequently, the Center is driven to develop a solution that *further translates* the VCF outputs from DRAGEN, making them more accessible and actionable for clinical use.

38 At the beginning of 2022, when I arrived at the Center to conduct this inquiry, the solution envisioned by the steering committee to address the usability issue was to acquire the proprietary software suite Congenica[16], an integrated platform for genomic analysis support, which has the advantage of being certified as a medical device under European legislation (and therefore easily integrable into the Center's accreditation extension request). Although this solution offers undeniable benefits – despite its relatively high cost – it places DRAGEN in an even more central position: since the VCF results generated by DRAGEN will then be transmitted to Congenica to make them more intelligible and actionable by clinicians, it becomes more important than ever to understand what happens inside DRAGEN. In short, at the start of 2022, with the imminent integration of Congenica to facilitate the interpretation of variant calling results, DRAGEN becomes more than ever one of the fragile obligatory passage points (Callon, 1984) in the Center's pipeline. Hence the importance, within the framework of its accreditation (and thus standardization) strategy, of knowing DRAGEN's capabilities in minute detail – that is, understanding both its strengths and its limitations.

DRAGEN versus GATK

39 A recent, proprietary, and costly software – because it requires dedicated hardware – DRAGEN constitutes a *grey box* (Latour, 2013, pp. 208-232): although its internal components are fairly well documented, its source code is not accessible, and at the time of the investigation, it does not have a large user community – unlike its main competitor, GATK, which is slower but more widely adopted. How, then, can one ensure that the VCF files rapidly produced by DRAGEN are robust enough for rWGS in the NICU and suitable for inclusion in the request to extend SAS accreditation? In March 2022, the Center's only available option is to carry out a comparative experiment between DRAGEN and GATK, the latter already being implemented and well understood by the bioinformaticians.

40 To this end, in late March 2022, Noah and Emily – two bioinformaticians of the Center's computation platform – designed a comparative experiment. This experiment was based on a recently received exploratory trio and a series of shell scripts they had written to identify all variant-calling differences between the two software suites[17]. It is this comparative experiment – central to the Center's strategy – that took place during

a working meeting held on the afternoon of Monday, March 28, 2022, that we will follow in detail in the remainder of this section. [18]

Initiating a qualitative comparison

41 All members of the computation platform team are present at this working meeting, which takes place – as it does every week – in the seminar room of the Center, within the Biomed park. Given the strategic importance of the main topic – the comparison between DRAGEN and GATK in preparation for the accreditation extension – Liam, the head of the sequencing platform, is also attending. As usual, the atmosphere is both serious and relaxed.

42 When it comes time to address the agenda item titled "DRAGEN versus GATK", Noah projects an .html document onto the room's screen, which will serve as a guide for the discussion on the comparative experiment he conducted with Emily:

> **Noah:** So we wrote a small script allowing us to compare the number of variants encoded by DRAGEN and by GATK, according to different quality thresholds [fig. 4][19]. And the first thing to see is that the number of variants remains quite close between the two. But these are absolute numbers; we are not yet talking about common variants.

Figure 4: The first two shell scripts written by Noah and Emily, allowing them to list the absolute number of variants for DRAGEN and GATK with different quality thresholds

DRAGEN with QUAL threshold = 40

```
# Number of retained variants
project=WGS_[redacted]_Jan22
analysisId=panelApp
cat $project\/$project\_variantSelection_$analysisId\.tsv | grep -v "^#" | wc -l
```

```
## 1490
```

GATK with QUAL threshold 40<=QUAL<=3000

```
for qual in 40 100 500 1000 1500 2000 2500 3000; do
    project=WGS_[redacted]_Jan22_GATK_QUAL$qual
    analysisId=panelApp
    nb=$(cat $project\/$project\_variantSelection_$analysisId\.tsv | grep -v "^#" | wc -l)
    echo -e "Qual_threshold=$qual\t$nb"
done
```

```
## Qual_threshold=40    1568
## Qual_threshold=100   1553
## Qual_threshold=500   1518
## Qual_threshold=1000  1492
## Qual_threshold=1500  1480
## Qual_threshold=2000  1468
## Qual_threshold=2500  1455
## Qual_threshold=3000  1444
```

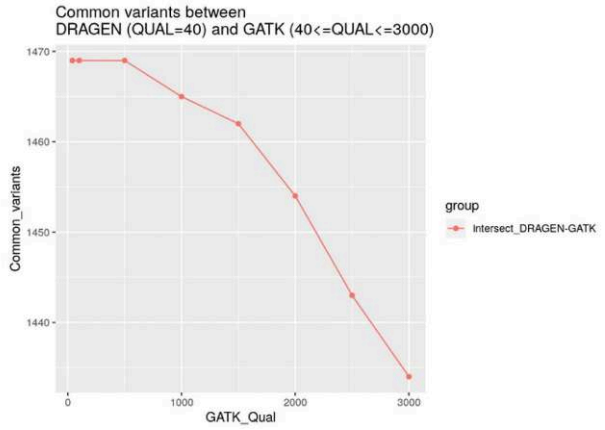
43 The shell script designed by Noah and Emily (fig. 4) provides a first comparative analysis of the number of variants identified by DRAGEN and GATK, based on different quality thresholds[20]. Unsurprisingly, adjusting the quality threshold in GATK – an option not available in DRAGEN – changes the number of variants detected, creating a discrepancy with those identified by DRAGEN. As Noah points out, although this initial observation is reassuring – the two tools detect a broadly similar number of variants – it remains incomplete. Indeed, it is limited to a simple absolute count, without indicating whether the variants are shared by both tools. To explore this question further, Noah introduces a second script:

Noah: And here you see the script that gives the evolution of the common variants according to the quality thresholds of GATK [fig. 5]. Basically, they start to diverge more seriously when GATK is set to 2000. Which is not a surprise because GATK starts to be very selective at that point. Again, this is pretty good because the number of common variants remain quite high even until that point. However, it doesn't give us any specific information about the unique variants.

Figure 5: Shell script written by Noah and Emily (upper part) producing a graph showing the evolution of common variants according to various GATK quality thresholds (lower part)

```
mkdir -p comp_GATK_Dragen_pannelApp
echo -e "GATK_Qual\tCommon_variants\tgroup" > comp_GATK_Dragen_pannelApp/intersect_dragen_gatk_QUAL40-3000.txt
for qual in 40 100 500 1000 1500 2000 2500 3000; do
    project=WGS_[redacted]Jan22_GATK_QUAL$qual
    # Compare GATK vs DRAGEN on th pannelApp regions
    comm -1 -2 <(cut -f1,2 $project/$project\_variantSelection_panelApp.tsv | tr '\t' '|' | sort) <(cut -f1,2 WGS
_[redacted]Jan22_v0.0.3/WGS_[redacted]Jan22_v0.0.3_variantSelection_panelApp.tsv | tr '\t' '|' | sort) > comp_GATK_
Dragen_pannelApp/GATK-QUAL$qual\_DRAGEN_intersection.txt
    intersect=$(cat comp_GATK_Dragen_pannelApp/GATK-QUAL$qual\_DRAGEN_intersection.txt | wc -l)
    echo -e "$qual\t$intersect\tintersect_DRAGEN-GATK" >> comp_GATK_Dragen_pannelApp/intersect_dragen_gatk_QUAL40
-3000.txt
done
```

```
library(ggplot2)
a = read.table("comp_GATK_Dragen_pannelApp/intersect_dragen_gatk_QUAL40-3000.txt", header=TRUE)
ggplot(data=a, aes(x=GATK_Qual, y=Common_variants, group=group)) + geom_line(aes(color=group)) + geom_point(aes(c
olor=group)) + ggtitle("Common variants between\nDRAGEN (QUAL=40) and GATK (40<=QUAL<=3000)")
```



44 Commenting on the graph in fig. 5, Noah explains that DRAGEN and GATK start to seriously diverge from the moment GATK is set at 2000. Before reaching that point – until the rather high-quality threshold of 1500, that is – the two programs seem to be roughly on the same page, which is a positive sign since GATK remains the gold standard, reliable and documented. However, this information is only indicative: there is still to consider the total number of variants that are either unique to DRAGEN or to GATK, and to verify that the 1500 threshold is indeed the breaking point between the two software suites:

Noah: And here [fig. 6] you see another more precise script which shows that it is in fact at threshold 1500 that we have the most common variants, but also the least unique variants. Forty-eight in this case.

Sam: Sorry but I don't understand why the DRAGEN curve decreases at some point..

Emily: That's because the GATK curve is increasing. And the third one [in green] is just the sum.

Sam: Ah ok I see.

Noah: And as we've learned from last time with SAS, we must deal with what doesn't work, but also highlight what does work. So we decided to focus on the quality of these forty-eight variants and the reasons why they are unique to each software.

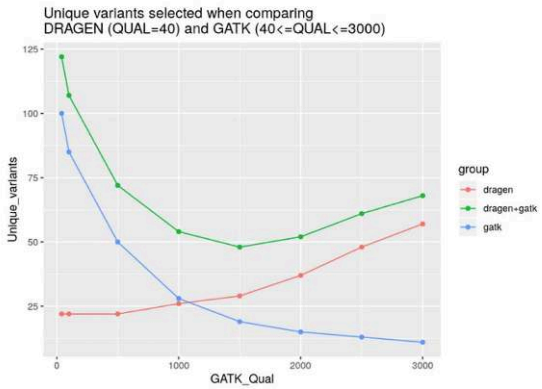
Ethan: Good.

Liam: Right.

Figure 6: Graph extracted from Noah's and Emily's shell code showing the evolution of unique GATK and DRAGEN variants according to different GATK quality thresholds

```
echo -e "GATK_Qual\tUnique_variants\tgroup" > comp_GATK_Dragen_pannelApp/diff_dragen_gatk_QUAL40-3000.txt
for qual in 40 100 500 1000 1500 2000 2500 3000; do
    project=WGS_[redacted]Jan22_GATK_QUAL$qual
    comm -3 <(cut -f1,2 $project/$project\_variantSelection_panelApp.tsv | tr '\t' '|' | sort) <(cut -f1,2 WGS_GC
_Kispi_Jan22_v0.0.3/WGS_[redacted]Jan22_v0.0.3_variantSelection_panelApp.tsv | tr '\t' '|' | sort) > comp_GATK_Dra
gen_pannelApp/GATK-QUAL$qual\_DRAGEN_diff.txt
    cat comp_GATK_Dragen_pannelApp/GATK-QUAL$qual\_DRAGEN_diff.txt | awk 'BEGIN{FS="\t"}{print $1}' | grep -v "
^$" > comp_GATK_Dragen_pannelApp/GATK-QUAL$qual\_unique.txt
    cat comp_GATK_Dragen_pannelApp/GATK-QUAL$qual\_DRAGEN_diff.txt | awk 'BEGIN{FS="\t"}{print $2}' | grep -v "
^$" > comp_GATK_Dragen_pannelApp/DRAGEN-QUAL$qual\_unique.txt
    gatk=$(cat comp_GATK_Dragen_pannelApp/GATK-QUAL$qual\_unique.txt | wc -l)
    dragen=$(cat comp_GATK_Dragen_pannelApp/DRAGEN-QUAL$qual\_unique.txt | wc -l)
    echo -e "$qual\t$gatk\tgatk" >> comp_GATK_Dragen_pannelApp/diff_dragen_gatk_QUAL40-3000.txt
    echo -e "$qual\t$dragen\tdragen" >> comp_GATK_Dragen_pannelApp/diff_dragen_gatk_QUAL40-3000.txt
    total=$(($gatk + $dragen))
    echo -e "$qual\t$total\tdragen+gatk" >> comp_GATK_Dragen_pannelApp/diff_dragen_gatk_QUAL40-3000.txt
done
```

```
library(ggplot2)
a = read.table("comp_GATK_Dragen_pannelApp/diff_dragen_gatk_QUAL40-3000.txt", header=TRUE)
ggplot(data=a, aes(x=GATK_Qual, y=Unique_variants, group=group)) + geom_line(aes(color=group)) + geom_point(aes(c
olor=group)) + ggtitle("Unique variants selected when comparing\nDRAGEN (QUAL=40) and GATK (40<=QUAL<=3000)")
```



45 The new inscription (fig. 6) confirms that the two software suites converge when GATK is set to quality 1500, with "only" forty-eight unique variants (twenty-nine unique to DRAGEN and nineteen unique to GATK). This is where a lesson – shared by Noah – comes into play, drawn from the Center's previous accreditation process for its 'wet part': during an SAS accreditation process, candidates must demonstrate that problematic results are addressed head-on, *while also highlighting operational and positive outcomes*. And it is by virtue of this lesson – confirmed by Ethan (head of the computation platform) and Liam (head of the sequencing platform) – that Noah and Emily decided to focus their experiment on these forty-eight unique variants, expressions of an a priori small but nonetheless real and potentially problematic discordance between DRAGEN and GATK.

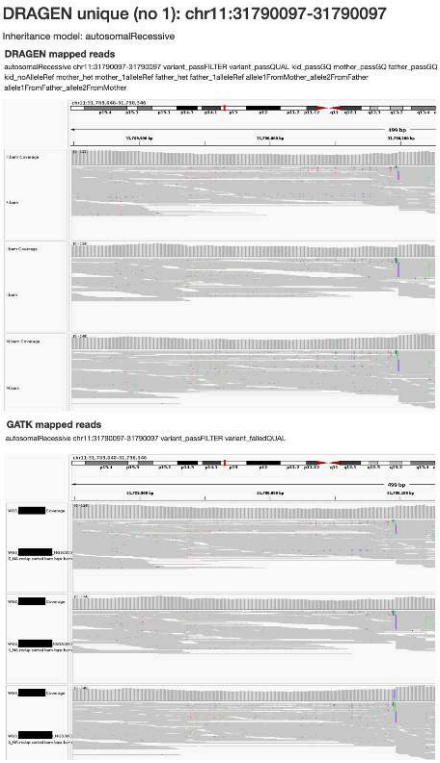
46 At this stage of the analysis, a first, basic but important observation can be made. Before Noah and Emily's shell scripts, DRAGEN and GATK were software tools that could only be compared quantitatively: they processed the same trio at very different speeds and produced results – namely genomic variants – that were slightly different. However, in order to initiate an evaluation for accreditation purposes, it here appears necessary to create the conditions for a *qualitative* comparison, one that focuses not only on the number of detected elements but also on the characteristics of their internal components. It is only once the forty-eight unique variants are known – in fact, *constructed* through scripts, graphs, and more or less strategic decisions – that Noah and Emily are truly able to begin the comparative experiment capable of identifying differences between the two software suites.

Identifying an issue

47 Let's continue to follow the same group meeting:

> **Noah**: And now, since we have the references of the variants, we can use IGV to see what is happening at the level of the BAMs for both DRAGEN or GATK. And it gives us this type of images that we can compare [fig. 7].

Figure 7: Excerpts from an IGV visualization of mismatches (colored dots) on the numerous reads (grey layers) of gene positions 31789800 (far left) to 31790200 (far right). The position 31790097 (horizontal succession of colored dots) is where the DRAGEN unique variant is called



48 Several things need to be clarified here. First, when a variant is identified, it is labelled with a standard 23-character reference (e.g., "chr11:31799997-31799997") that indicates where this variant appears in the genome. From this information, it is then possible to consult the BAM data – i.e., the sequences of the patients aligned to the unique Genome in a Bottle reference[21] – as generated by DRAGEN and GATK and which serve as a basis for encoding, or not, the variants. Important note: each of the billions of nucleotide bases (i.e., letters "A", "C", "G", or "T") is identified not from a single fragment (this would generate a considerable risk of error), but from numerous fragments called reads, which form a layer of variable thickness (grey strata in fig. 7). Each nucleotide is therefore identified several times – and sometimes differently – at each position of the genome, and it is up to the variant calling software – set manually by the bioinformatician – to define whether there is variation or not, based on what is indicated on these layered reads. And to obtain a simultaneous visualization of all this (reads, nucleotides, variations), it is necessary to use another dedicated software package, in this case IGV, which highlights the mismatches by different color codes. The idea of Noah and Emily is thus to visualize via IGV[22] the locations of the forty-eight

unique variants of GATK and DRAGEN in order to try to infer the reasons behind their respective calls.

49 With these clarifications in mind, let's continue to follow the meeting:

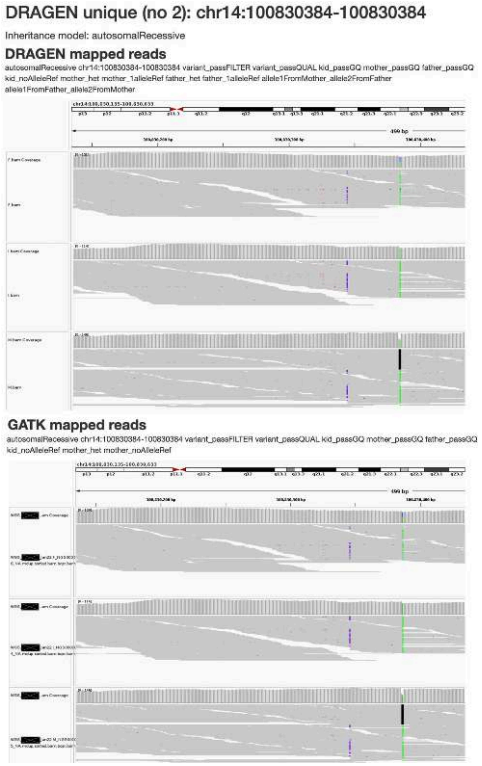
> **Noah**: And what we noticed is that there are two categories of unique variants. The first one is what we see here [figure 8]. It's not easy to see, but there are lots of coloured dots all over the place, and that means that there are lots of mismatches here ongoing. So it's a typical example of a region that is problematic to map. Basically, the callers [i.e., DRAGEN and GATK] do what they can in this region; one is calling something, and the other is calling something else. But the called variants are problematic anyway.
> **Ethan**: It's true that this is a notoriously problematic region, here.
> **Sam**: Yes, and they are plenty of these low complexity regions.
> **Emily**: So it's not really a mistake. There's nothing you can really do about it.

50 Some regions of the genome are difficult to map – i.e., to describe in terms of their nucleotides – because they are of low complexity, made of repetitions of the same nucleotides (e.g., 'AAAAAA'), that is. Counter-intuitively, these regions are prone to numerous description errors, as the absence of any reference points limits computational control and correction operations[23]. As a result, these regions – well known to bioinformaticians working in genomics – tend to lead to more mismatches, which, by accumulation, can sometimes be called as variants. For what interests the Center here, this information, although important, does not require more careful consideration: whether they are encoded solely by DRAGEN or by GATK, these variants must in any case be considered with suspicion by the analyst in charge of the data delivery, because chances are high that they are simply artifacts resulting from alignment errors due to the low quality of the "raw" sequences. In short, this is a classic problem, common across the field of contemporary computational genomics, and one that the Center, as things stand, cannot do much about.

51 So far, then, the comparison experiment is going rather well: the number of unique variants is relatively low and, for a part of them, these differences are due to well-known "regional" sequencing problems that cannot be solved as it is. However, the second reason discussed by Noah and Emily will prove to be more problematic:

> **Noah:** The other issue that we need to discuss is related to the way the VCF is encoded. Because there seems to be sometimes a difference between GATK and DRAGEN that could be a bit misleading. You can see an example here [fig. 8], but you have the complete list in the document. So here [fig. 8] we are looking at an autosomal recessive variant and you can see that there are substitutions marked in green in the father [the first IGV row], the mother [last IGV row] and the child [middle IVG row]. But in the mother, there's also a whole part that is not green, which is actually a deletion. But DRAGEN doesn't mention it in the VCF.
> **Ethan:** And what about GATK?
> **Noah:** This is the problem because GATK maps the location the same way, calls the substitution but also mentions the possibility of the deletion. This is why you have two different variants at the same position. But I agree, it's difficult to see that on that image.

Figure 8: Excerpts from IGV illustrating called mismatches (colored dots) on the numerous reads (grey layers) of gene positions 100830100 (far left) to 100830500 (far right). The position 100830384 (horizontal succession of green dots) is where the DRAGEN unique variant is called



52 The second reason for the dissimilarities between GATK – the gold standard – and DRAGEN seems trickier. In the case examined by Noah (fig. 8), it seems that DRAGEN only considers the possibility of a substitution and ignores the possibility of a deletion, which is obvious – for trained bioinformaticians – when looking at the details of the BAM data via IGV. This omission is all the more problematic as the VCF format allows to suggest both possibilities (substitution or deletion), which GATK does in an expected way. What is going on inside DRAGEN that makes it "forget" the possibility of a deletion, even though this could be problematic in an rWGS for NICU context where every variant matters[24]? Difficult to know at this stage, for as the IGV visualization remains at a too high level. It seems therefore important to zoom in further:

> **Noah:** But when you zoom in IGV [fig. 9], you see that the deletion starts at the previous position, that is "383" [chr14 100830383]. You can also see that in the detail of the VCF [fig. 10] where it is noted "ACC/A". But at the next position [chr14 100830384], DRAGEN mentions only the "CA" substitution while GATK also mentions the possible "*" deletion. We found this in twenty cases, but we don't know why DRAGEN does that.

Figure 9: IGV zoom on position 100830384 (far right) as mapped by DRAGEN

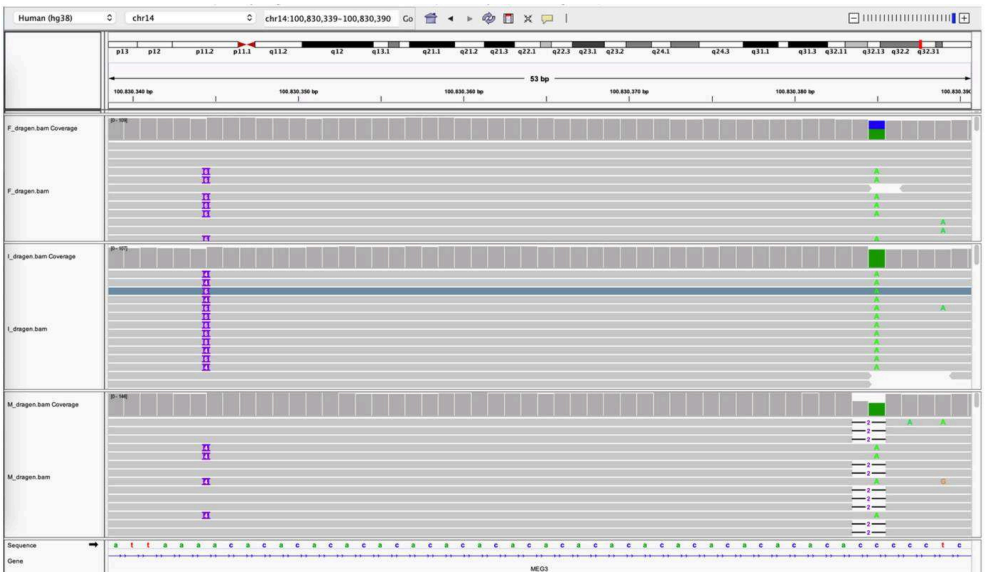


Figure 10: Extracts of VCF files as encoded by DRAGEN (upper half) and GATK (lower half) between positions 100830374 and 100830394. For both programs, only positions 100830383 to 100830385 are concerned by this calling, though in a slightly different way

```
        @frt2 ICU_variantSelection]$ bcftools view -H -r chr14:100830374-100830394 /data/UHTS/us
 | cut -f1-7,10- | sed 's/:[^\t]*//g'
chr14   100830383       .       ACC     A       45.23   PASS    0/0     0/0     0|1
chr14   100830384       .       C       CA      363.69  PASS    0|1     1/1     1|0
chr14   100830385       .       C       CACA,CACACA     243     PASS    0|2     1/2     1|0
        @frt2 ICU_variantSelection]$ #GATK
        @frt2 ICU_variantSelection]$ bcftools view -H -r chr14:100830374-100830394 /scratch/perm
8631309.genotyped.vcf.gz | cut -f1-7,10- | sed 's/:[^\t]*//g'
chr14   100830383       rs1491366505    ACC     A       944.25  PASS    0/0     0/0     0/1
chr14   100830384       rs373934045     C       CA,*    5481.75 PASS    0/1     1/1     1/2
chr14   100830385       .       C       CACACA,CACA,*   5196.29 PASS    0/1     1/2     2/3
        @frt2 ICU_variantSelection]$
```

53 The problem is becoming clearer, but remains open. Indeed, when zooming in IGV, it appears that the possible deletion occurs – for some reads – at position "100830383" (fig. 9). Then, upon examining the VCF file generated by DRAGEN (fig. 10, top section), only the substitution of 'C' – the reference base – with 'A' is reported. In contrast, GATK (fig. 10, bottom section) reports not only this substitution but also flags the potential deletion, represented by an '*' at position "100830384". This appears to be a notable discrepancy that warrants closer examination.

54 At this slightly more advanced stage of the analysis, a second observation can be made. Thanks to an experimental setup that includes details of the VCF files and accurate visualizations of the BAM files via IGV, Noah and Emily manage to define a problematic phenomenon: under rare conditions, DRAGEN fails to encode deletions while GATK manages to do it. As a result, twenty unique DRAGEN variants are of *lower quality* than those of GATK because they do not include the possibility of deletions in addition to likely substitutions. A problem is thus *realized* – in the sense of made real – while being marginalized – in the sense of being related to numerous alignments. Did this problem exist before the comparative analysis? Most likely, but it remained latent and unnoticed. The experiment, by revealing its existence, provides the opportunity to better characterize it.

Elaborating an opportunity

55 What is the reason for DRAGEN's non-notification of possible deletions, which explains the existence of a significative proportion – although modest in absolute numbers – of unique variants (twenty out of forty-eight)?

> **Noah**: Actually, it seems that when a deletion occurs at a position prior to a substitution, DRAGEN fails to include it in the VCF.
> **Ethan**: It could be a bug?
> **Sam**: Maybe. But what's weird is that it seems to be a problem in the way DRAGEN encodes the VCF. Because the mapping is similar to GATK.
> **Noah**: That's what we thought too.
> **Ethan**: So is there any way to ask DRAGEN to consider the prior position before encoding?
> **Emily**: Certainly, it's imaginable. But it would be necessary to dig deeper to better frame and specify the problem. For example, is it only one position prior, or several? And is it only in specific regions?

56 The exact reason why DRAGEN does not consider possible deletions that start at positions prior to substitutions seems difficult to isolate. It may be a bug or a bad setting. But is it possible to set up an ad hoc solution – for example by means of a dedicated script – to ask DRAGEN to take into account these cases of possible deletions? For Emily, who participated in the installation and fine-tuning of DRAGEN, this seems doable. But the problem still needs to be better defined, which would require further tests and experiments. And is it really worth it?

> **Ethan**: Okay, it's important to remember what we talked about last time: we are asked to know our limits.
> **Liam**: Voilà, exact. Ils [les SAS] s'attendent pas à ce que nous soyons parfaits. Ils attendent de nous des résultats convaincants, mais aussi qu'on souligne les imperfections de nos résultats. Et à partir du moment où on montre qu'on a aussi des idées pour améliorer les choses, c'est considéré comme positif.
> **Ethan**: Yes, exactly. They [the SAS] don't expect us to be perfect. They expect us to show convincing results but also to point out the imperfections of our results. And as long as we show that we also have ideas on how to improve things, it's considered positive.
> ...
> **Liam**: Yes. And that's also what they [the SAS] are looking for, because the ISO doesn't give much in terms of geekery.
> **Ethan**: So we've got some leeway, but we need to choose carefully what to say.

57 The compromise proposed by Ethan - based on exchanges within the team - is to leave it at that for the time being, integrating the comparative experiment and its results into the application for the accreditation extension. What we may call the DRAGEN's deletion problem concerns less than 2% of the variants, and the Center has the ressources and competences to correct this later. Strategically, the decision seems to make sense: it is indeed crucial for the Center to project itself beyond the accreditation extension, taking into account the biannual audits that will verify the pipeline's compliance, while evaluating the improvements made or not. And this DRAGEN problem, previously made real and marginal, could even be a hold to work towards maintaining the accreditation (if it is granted to the dry part of the Center).

58 Interestingly, we can see here that the experience gained during the previous accreditation process is a resource for turning DRAGEN's deletion problem into an

opportunity. Indeed, according to Ethan and Liam – who both participated in the accreditation of the Center's wet part – a common misunderstanding is to consider an accreditation request as a requirement for perfect results. But the reality is more subtle (and interesting): the SAS, as surely other accreditation bodies, places greater importance on the means available to control and improve the reliability of perfectible results over time. This insider tip, which derives from the previous accreditation past experiences, allows the Center to turn the situation around. Indeed, what emerged from Noah et Emily's comparative experiment may be less a touchy problem than a strategic opportunity: looking at it from the other end of the spectrum (made possible by prior experience), the deletion problem *becomes* evidence of the Center's ability to identify subtle limitations in its pipeline, while also outlining concrete avenues for improvement – a process typically viewed positively by the SAS.

59 In fact, it is all the more important for the Center to suggest concrete avenues for improvement, given that ISO 15189 – the standard on which the SAS accreditation is based – remains rather allusive when it comes to quality criteria for computational elements in biomedical laboratories, as Liam points out at the end of the excerpt ("ISO doesn't give much"). The strategy of being generous to the SAS by presenting them with a well-constructed, improvable problem thus seems promising, without offering any guarantees, as Ethan immediately points out ("but we need to choose carefully what to say").

60 All in all, the careful account of this comparative experiment seems to indicate that one stake – certainly among many others – of the preparation for an accreditation trial in computational genomics may lie in the adequate construction of qualitative problems large enough to be identified and assessed, but also small (or *made* small) enough to enable short-term resolutions. Rather than a demonstration exercise (Rosental, 2009), it is an effort to highlight surmountable limitations in order to show, in turn, the potential for continuous improvement.

61 In this sense, far from being a mechanical or merely administrative procedure, the preparation for an accreditation trial in computational genomics appears to be a subtle form of creative work that involves highlighting the limits of one's system by virtue of the subsequent improvements that might be made to it. In this sense, far from being a mechanical or merely administrative procedure, the preparation for an accreditation trial in computational genomics appears to be a subtle form of creative work that involves highlighting the limits of one's system by virtue of the subsequent improvements that might be made to it. Part of what we might call the art of accreditation, and perhaps of standardization processes in general, seems to lie in this ability to shape and valorize problems that are at once real, marginal, and correctable. This work of adjusting, reframing, and reformulating problems echoes what Joan Fujimura (1987) calls *doability*, understood as the ability to make a project feasible in a given socio-technical context. Accreditation thus becomes not only a trial of conformity, but also a moment when one strategically reconfigures the conditions of a system's feasibility, making it both problematizable and improvable.

Acceleration and influence

62 The session ends with Ethan's compromise: the preparatory experiment, with a few minor adjustments, can be incorporated almost as it stands into the application for

accreditation. It will thus constitute the central element – albeit imperfect, but this is precisely one of the goals – of the chapter devoted to variant calling. Does this mean that this working meeting was the key step in the accreditation process for the computation platform? No, because the accreditation – and therefore the trial through which it goes and which requires so much preparation – also concerned other important elements, notably in connection with data protection and cybersecurity, which themselves required major preparatory efforts (not documented here). But in a sense, yes, because among the chapters essential to the elaboration of the preparatory report for accreditation – covering cybersecurity, traceability, data protection, etc. – the question of the quality of rapid variant calling was central to the Center's semi-commercial efforts (cf. above), while being unquestionably the least well-defined within the ISO standard, and therefore also within the SAS evaluation criteria. In other words, the necessary chapter dedicated to variant calling was both the one with the fewest guidelines and the one that played one of the leading roles in the Center's future strategy, and this very contradiction represented a theoretical and practical challenge, finally overcome *in situ* at this working session.

63 But did all this work? Did the preparatory efforts of the computation platform's bioinformaticians to patiently define DRAGEN's strengths and limitations for variant calling pay off? Absolutely, so much so that the whole accreditation extension procedure has even been accelerated, notably to enable some members of the computation platform to take part in audits of other Swiss genomics centers. In short, the innovations produced by the Center in terms of quality control, and in particular with regard to variant calling, have ended up being integrated into the SAS criteria, in particular to help specify and reinforce the ISO 15189 standard with regard to these highly technical but also quite common aspects of computational genomics.

64 Unfortunately, the data collected in this study do not allow us to pinpoint any specific reasons for the SAS's decision, but they do indicate that an acceleration did indeed take place, as the SAS was finally quick to extend the Center's accreditation to its dry part. Unfortunately, the data collected in this study do not allow us to pinpoint any specific reasons for the SAS's decision, but they do indicate that an acceleration did indeed take place, as the SAS was finally quick to extend the Center's accreditation to its dry part[25]. But also, by now being "physically" part of the SAS evaluation criteria, the Center has increased its influence within the Swiss genomics ecosystem. In sum, the Center has succeeded in articulating the ISO 15189 quality standard to the asperities of its computational equipment, accurately anticipating SAS expectations and its room for maneuver on cutting-edge bioinformatics issues.

Discussion and conclusion

65 Rather surprisingly, little has been said in the socio-anthropological literature about the accreditation or certification (and therefore standardization) trials in computational genomics, even though these trials constitute obligatory passage points for anyone wishing to develop 'personalized' or 'precision' clinical medicine, itself the object of numerous utopian and dystopian discourses (e.g., Roth & Bruni, 2021; Topol, 2019; Zuboff, 2019, chap. 8). Maybe this is due to the ethnographic posture this field-based analysis requires, which implies getting in close contacts with bioinformaticians to observe – quite intrusively, to be fair – their mundane practices, particularly those of

preparing for costly and often crucial examinations? From the perspective of a sociology of the preparation for standardization trials in bioinformatics, this article intends to propose some fragile but real foundations for such an exploration. By way of conclusion, at the end of this dive to the heart of bioinformatics in action, I would like to discuss three observations.

66 The first observation confirms a phenomenon already documented in the literature: the inevitable need to "tinker" with the standard (Timmermans & Epstein, 2010; Lampland & Star, 2008). This is particularly obvious in the case of the Center, which has no choice but to adopt an active stance towards the ISO 15189 standard, whose conformity is inspected by the SAS. Indeed, this standard does not explicitly specify the quality criteria applicable to advanced bioinformatics elements related to variant calling. This vagueness, legacy of the pre-computational genomics era, obliges the Center to frame the standard while complying with it – a craftsman's task as much as an exercise in rigor. This seeming contradiction, which is resolved in practice, echoes Timmermans and Epstein's observation that "to coordinate diverse interests and activities, standards necessarily delegate some residual work that requires active participation and submission of people to the standard's directives" (2010, p. 81). Thus, far from being merely a regulatory constraint, the Center's appropriation of the standard illustrates the broader dynamic of adaptation and negotiation inherent in standardization in a technoscientific and biomedical context.

67 The second observation highlights the inherent ambivalence of standardization processes. They are not simply directives imposed from above, exerting domination over practitioners, as one might intuitively think. They can also be seized from below, offering actors genuine strategic opportunities, as Timmermans and Almeling (2009) had already pointed out in the context of hospital care. In the case of the Center, the strategic dimension of the accreditation process is evident, at least when examined closely. Indeed, it enables the Center, at least theoretically, to enter a market whose semi-commercial economic returns are crucial to its sustainability and development. This reality of the computational genomics sector in Switzerland even suggests that the argument put forward by Webster and Eriksson (2008) about governance by standards needs to be somewhat nuanced. Indeed, if a form of governance does exist, it derives not so much from standardization bodies – ISO or SAS, which remain relatively vague about the computational aspects of medical laboratories in Switzerland – as from some players of the sector, such as the Center itself, who rely on a standard and the quality label associated with its accreditation to establish their position in a competitive environment. The extension of the Center's accreditation to its genomic analyses of trio is a striking and successful illustration of this: this standardization process ended up establishing the Center as a benchmark by setting a precedent. From now on, any laboratory wishing to obtain accreditation for genomic analyses will have to draw inspiration from the work carried out by the Center (and therefore, ultimately, from its instruments), which will serve as the initial model retained by the SAS.

68 Finally, on a more anthropological level, this inquiry also enriches the social study of preparation (Riom & Tanferri, 2024), by documenting a specific mode of preparatory action, which revolves around three moments: a properly epistemic moment, a moment of negative criticism and a moment of positive orientation. Taking a quick look back at the Center's preparatory session, the role of bioinformaticians Noah and Emily was at first essentially to set up a comparative experiment to better understand

the behavior of the new proprietary DRAGEN software suite, as integrated into the Center's pipeline. The practices involved at this preliminary stage – obtaining a trio of samples, analyzing them with both DRAGEN and GATK (the slower reference in the field), then writing several shell scripts to compare their results – can thus be described as *epistemic*, insofar as they aimed to shed light on DRAGEN's constitutive relationships. However, as we have seen, once the experiment aimed to inform DRAGEN's behavior had been established, the positive results had to be bracketed to better focus on the problematic ones. In this case, while the high number of common variants between DRAGEN and GATK was a relief for the Center, what really mattered were the few dozen unique variants, expressions of marginal but real discordances. The attention paid to malfunctions appears here to be a central issue: it does not matter whether the device works in the vast majority of cases, what really counts is the ability to identify anomalies and failures. Here, bioinformaticians seem to have to make a switch from an initial epistemic mode – undoubtedly essential – to what I call a negative-critical mode, just as essential but arguably less intuitive, where attention is focused mainly on limitations and malfunctions. But merely pointing out dysfunctions would not be enough to meet the requirements of a preparation for a standardization trial in computational genomics. In view of the elements presented, it is still important to succeed in presenting what resists as something that can be improved and, ideally, resolved. And it is precisely here that a positive approach seems necessary, aimed at deriving benefits from the problematic situation that has been attested. In the case presented here, DRAGEN had some difficulty in including in its VCFs the possibility of deletions when they preceded and overlapped with possible substitutions. But the Center's bioinformaticians, aided by the experience accumulated during the previous accreditation process, managed to turn the situation to their advantage by presenting it as an opportunity to make their pipeline even more efficient, in their now perpetual quest – at demand from the SAS – for process improvement. So it turns out that part of what we might call the art of standardization processes lies, perhaps and sometimes, in this ability to shape and enhance *doable* problems (Fujimura, 1987) that are at once real, marginal, and correctable.

69 These three elements – the tinkering with standards, their ambivalence, and the modes of action specific to the preparation of trials – are still provisional results, drawn from a case study carried out in a particular national context. Further inquiries are obviously needed to gain a better understanding of the driving forces behind the preparation of standardization trials, in bioinformatics and elsewhere. But I hope that the present analysis offers a glimpse of some concrete, albeit surreptitious, aspects of the close links between bioinformatics and standardization processes, beyond the abstractions that feed utopian and dystopian discourses on the advent of so-called personalized or precision medicine.

This work was supported by the SNSF Sinergia 180350 research fund, « Development of Personalized Health in Switzerland: Social Sciences Perspectives ». I would like to express my deep gratitude to the members of the Computational Genomics Center who allowed me to follow their activities and, more generally, helped me in my research. My gratitude also goes to Geoffrey Bowker, Nolwenn Bühler, Luca Chiapperino, Nils Graber, Francesco Panese, Dominique Vinck, the anonymous reviewers, and the editors of this journal for their support, assistance, and insightful suggestions. Any errors or inaccuracies remain, of course, my sole responsibility.

BIBLIOGRAPHY

Australian Genomics Health Alliance Acute Care Flagship. (2020). Feasibility of Ultra-Rapid Exome Sequencing in Critically Ill Infants and Children With Suspected Monogenic Conditions in the Australian Public Health Care System. *JAMA*, *323*(24), 2503-2511. https://doi.org/10.1001/jama.2020.7671

Bowker, G. C. & Star, S. L. (2000). *Sorting Things Out: Classification and Its Consequences*. Cambridge, Mass. : The MIT Press.

Busch, L. (2013). *Standards: Recipes for Reality*. Cambridge, Mass. : MIT Press.

Callon, M. (1984). Some Elements of a Sociology of Translation: Domestication of the Scallops and the Fishermen of St Brieuc Bay. *The Sociological Review*, *32*(1), 196-233. https://doi.org/10.1111/j.1467-954X.1984.tb00113.x

Callon, M. (2021). *Markets in the Making: Rethinking Competition, Goods, and Innovation*. Brooklyn/New York : Zone Books.

Callon, M., Cohendet, P., Curien, N. & Dalle, J.-M. (1999). *Réseau et coordination*. Paris : Economica.

Cambrosio, A. & Keating, P. (1992). A Matter of FACS: Constituting Novel Entities in Immunology. *Medical Anthropology Quarterly*, *6*(4), 362-384. https://doi.org/10.1525/maq.1992.6.4.02a00040

Cambrosio, A., Keating, P., Schlich, T. & Weisz, G. (2006). Regulatory objectivity and the generation and management of evidence in medicine. *Social Science & Medicine*, *63*(1), 189-199. https://doi.org/10.1016/j.socscimed.2005.12.007

Casper, M. J. & Clarke, A. E. (1998). Making the Pap Smear into the 'Right Tool' for the Job: Cervical Cancer Screening in the USA, circa 1940-95. *Social Studies of Science*, *28*(2), 255-290. https://doi.org/10.1177/030631298028002003

Chiapperino, L., Graber, N. & Panese, F. (2024). A precision immuno-oncology turn? Hybridizing cancer genomics and immunotherapy through neoantigens-based adoptive cell therapies. *Social Studies of Science*, 03063127241303720. https://doi.org/10.1177/03063127241303720

Clark, M. M., Hildreth, A., Batalov, S., Ding, Y., Chowdhury, S., Watkins, K., Ellsworth, K., Camp, B., Kint, C. I., Yacoubian, C., Farnaes, L., Bainbridge, M. N., Beebe, C., Braun, J. J. A., Bray, M., Carroll, J., Cakici, J. A., Caylor, S. A., Clarke, C., … Kingsmore, S. F. (2019). Diagnosis of genetic diseases in seriously ill children by rapid whole-genome sequencing and automated phenotyping and interpretation. *Science Translational Medicine*, *11*(489), eaat6177. https://doi.org/10.1126/scitranslmed.aat6177

Conley, T. (1998). Mapping in the Folds: Deleuze « Cartographe ». *Discourse*, *20*(3), 123-138. https://www.jstor.org/stable/41389502 (consulted on July 18, 2025)

Dear, P. & Jasanoff, S. (2010). Dismantling boundaries in science and technology studies. *Isis; an International Review Devoted to the History of Science and Its Cultural Influences*, *101*(4), 759-774.

Desrosières, A. (2000). *La politique des grands nombres. Histoire de la raison statistique*. Paris : La Découverte.

Dimmock, D., Caylor, S., Waldman, B., Benson, W., Ashburner, C., Carmichael, J. L., Carroll, J., Cham, E., Chowdhury, S., Cleary, J., D'Harlingue, A., Doshi, A., Ellsworth, K., Galarreta, C. I.,

Hobbs, C., Houtchens, K., Hunt, J., Joe, P., Joseph, M., … Farnaes, L. (2021). Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. *The American Journal of Human Genetics*, *108*(7), 1231-1238. https://doi.org/10.1016/j.ajhg.2021.05.008

Edwards, P. N., Mayernik, M. S., Batcheller, A. L., Bowker, G. C. & Borgman, C. L. (2011). Science friction: Data, metadata, and collaboration. *Social Studies of Science*, *41*(5), 667-690. https://doi.org/10.1177/0306312711413314

Farnaes, L., Hildreth, A., Sweeney, N. M., Clark, M. M., Chowdhury, S., Nahas, S., Cakici, J. A., Benson, W., Kaplan, R. H., Kronick, R., Bainbridge, M. N., Friedman, J., Gold, J. J., Ding, Y., Veeraraghavan, N., Dimmock, D. & Kingsmore, S. F. (2018). Rapid whole-genome sequencing decreases infant morbidity and cost of hospitalization. *npj Genomic Medicine*, *3*(1), 1-8. https://doi.org/10.1038/s41525-018-0049-4

Federal Act on Human Genetic Testing, 810.12, CH, (2004). Available at à https://www.fedlex.admin.ch/eli/cc/2007/131/en (consulted on October 8, 2023)

Federal Act on Medically Assisted Reproduction, 810.11, CH, (1998). Available at https://www.fedlex.admin.ch/eli/cc/2000/554/en (consulted on October 8, 2023)

Foucault, M. (1963). *Naissance de la clinique. Une archéologie du regard médical.* Paris : Presses universitaires de France.

Foucault, M. (1975). *Surveiller et punir : Naissance de la prison* (French Language édition). Paris : Gallimard.

Fujimura, J. H. (1987). Constructing 'Do-able' Problems in Cancer Research: Articulating Alignment. *Social Studies of Science*, *17*(2), 257-293. https://doi.org/10.1177/030631287017002003

GATK Team. (2024, june 25). *Phred-scaled quality scores*. GATK. https://gatk.broadinstitute.org/hc/en-us/articles/360035531872-Phred-scaled-quality-scores (consulted on July 18, 2025)

Hà, T.-D. & Chow-White, P. A. (2021). The cancer multiple: Producing and translating genomic big data into oncology care. *Big Data & Society*, *8*(1), 2053951720978991. https://doi.org/10.1177/2053951720978991

Jarvis, E. D., Formenti, G., Rhie, A., Guarracino, A., Yang, C., Wood, J., Tracey, A., Thibaud-Nissen, F., Vollger, M. R., Porubsky, D., Cheng, H., Asri, M., Logsdon, G. A., Carnevali, P., Chaisson, M. J. P., Chin, C.-S., Cody, S., Collins, J., Ebert, P., … Miga, K. H. (2022). Semi-automated assembly of high-quality diploid human reference genomes. *Nature*, *611*(7936), 519-531. https://doi.org/10.1038/s41586-022-05325-5

Jaton, F. (2017). We get the algorithms of our ground truths: Designing referential databases in digital image processing. *Social Studies of Science*, *47*(6), 811-840. https://doi.org/10.1177/0306312717730428

Jaton, F. (2019). « Pardonnez cette platitude » : de l'intérêt des ethnographies de laboratoire pour l'étude des processus algorithmiques. *Zilsel*, *5*(1), 315-339. https://www.cairn.info/revue-zilsel-2019-1-page-315.htm

Jaton, F. (2021). Assessing biases, relaxing moralism: On ground-truthing practices in machine learning design and application. *Big Data & Society*, 8(1), 20539517211013569. https://doi.org/10.1177/20539517211013569

Jaton, F. (2021). *The Constitution of Algorithms: Ground-Truthing, Programming, Formulating*. Cambridge, Mass. : MIT Press.

Jaton, F. (2022). Éléments pour une sociologie de l'activité de programmation. *RESET. Recherches en sciences sociales sur Internet*, 11, 1-32. https://doi.org/10.4000/reset.3829

Jaton, F. (2023). Groundwork for AI: Enforcing a benchmark for neoantigen prediction in personalized cancer immunotherapy. *Social Studies of Science*, *53*(5), 787-810. https://doi.org/10.1177/03063127231192857

Jaton, F. & Vinck, D. (2016). Processus frictionnels de mises en bases de données. *Revue d'anthropologie des connaissances*, *10*(4), 489-504. https://doi.org/10.3917/rac.033.0489

Jaton, F. & Vinck, D. (2023). Politicizing Algorithms by Other Means: Toward Inquiries for Affective Dissensions. *Perspectives on Science*, *31*(1), 84-118. https://doi.org/10.1162/posc_a_00582

Kingsmore, S. F., Cakici, J. A., Clark, M. M., Gaughran, M., Feddock, M., Batalov, S., Bainbridge, M. N., Carroll, J., Caylor, S. A., Clarke, C., Ding, Y., Ellsworth, K., Farnaes, L., Hildreth, A., Hobbs, C., James, K., Kint, C. I., Lenberg, J., Nahas, S., … Yamada, C. (2019). A Randomized, Controlled Trial of the Analytic and Diagnostic Performance of Singleton and Trio, Rapid Genome and Exome Sequencing in Ill Infants. *The American Journal of Human Genetics*, *105*(4), 719-733. https://doi.org/10.1016/j.ajhg.2019.08.009

Kohler, R. E. (1994). *Lords of the Fly: Drosophila Genetics and the Experimental Life*. Chicago : University of Chicago Press.

Lampland, M. & Star, S. L. (dir.). (2008). *Standards and Their Stories: How Quantifying, Classifying, and Formalizing Practices Shape Everyday Life*. Ithaca : Cornell University Press.

Latour, B. (1987). *Science in Action – How to Follow Scientists & Engineers Through Society*. Cambridge, Mass. : Harvard University Press.

Latour, B. (2013). *An Inquiry Into Modes of Existence*. Cambridge, Mass. : Harvard University Press.

Lefebvre, M. (2013). L'infra-ordinaire de la recherche. Écritures scientifiques personnelles, archives et mémoire de la recherche. *Sciences de la société*, *89*, 3-17. https://doi.org/10.4000/sds.203

Mallard, A. (1998). Compare, Standardize and Settle Agreement: On some Usual Metrological Problems. *Social Studies of Science*, *28*(4), 571-601. https://doi.org/10.1177/030631298028004003

Mitchell, K., Brito, J. J., Mandric, I., Wu, Q., Knyazev, S., Chang, S., Martin, L. S., Karlsberg, A., Gerasimov, E., Littman, R., Hill, B. L., Wu, N. C., Yang, H. T., Hsieh, K., Chen, L., Littman, E., Shabani, T., Enik, G., Yao, D., … Mangul, S. (2020). Benchmarking of computational error-correction methods for next-generation sequencing data. *Genome Biology*, *21*(1), 71. https://doi.org/10.1186/s13059-020-01988-3

Nelson, N. C., Keating, P. & Cambrosio, A. (2013). On being "actionable": clinical sequencing and the emerging contours of a regime of genomic medicine in oncology. *New Genetics and Society*, *32*(4), 405-428. https://doi.org/10.1080/14636778.2013.852010

O'Connell, J. (1993). Metrology: The Creation of Universality by the Circulation of Particulars. *Social Studies of Science*, *23*(1), 129-173. https://doi.org/10.1177/030631293023001005

Owen, M. J., Lefebvre, S., Hansen, C., Kunard, C. M., Dimmock, D. P., Smith, L. D., Scharer, G., Mardach, R., Willis, M. J., Feigenbaum, A., Niemi, A.-K., Ding, Y., Van Der Kraan, L., Ellsworth, K., Guidugli, L., Lajoie, B. R., McPhail, T. K., Mehtalia, S. S., Chau, K. K., … Kingsmore, S. F. (2022). An automated 13.5 hour system for scalable diagnosis and acute management guidance for genetic diseases. *Nature Communications*, *13*(1), 4057. https://doi.org/10.1038/s41467-022-31446-6

Peerbaye, A. & Vinck, D. (2023). Les ethnographies de laboratoire : par-delà un mythe fondateur des STS. Dans S. Boudia & A. Peerbaye (dir.) *Sciences et techniques en sociétés* (p. 35-58). Paris : ISTE Éditions.

Petrikin, J. E., Willig, L. K., Smith, L. D. & Kingsmore, S. F. (2015). Rapid whole genome sequencing and precision neonatology. *Seminars in Perinatology*, *39*(8), 623-631. https://doi.org/10.1053/j.semperi.2015.09.009

Pfeifer, S. P. (2017). From next-generation resequencing reads to a high-quality variant data set. *Heredity*, *118*(2), 111-124. https://doi.org/10.1038/hdy.2016.102

Riom, L. & Tanferri, M. (2024). On the Trail of Preparations. *Revue d'anthropologie des connaissances*, *18*(2). https://doi.org/10.4000/11r9s

Rip, A. (1986). Controversies as Informal Technology Assessment. *Knowledge*, *8*(2), 349-371. https://doi.org/10.1177/107554708600800216

Robinson, J. T., Thorvaldsdóttir, H., Winckler, W., Guttman, M., Lander, E. S., Getz, G. & Mesirov, J. P. (2011). Integrative genomics viewer. *Nature Biotechnology*, *29*(1), 24-26. https://doi.org/10.1038/nbt.1754

Rosental, C. (2009). Anthropologie de la démonstration. *Revue d'anthropologie des connaissances*, *32*(2), 233-252. https://doi.org/10.3917/rac.007.0233

Roth, P. H. & Bruni, T. (2021). Participation, Empowerment, and Evidence in the Current Discourse on Personalized Medicine: A Critique of "Democratizing Healthcare". *Science, Technology, & Human Values*, 01622439211023568. https://doi.org/10.1177/01622439211023568

Stevens, H. (2013). *Life Out of Sequence: A Data-Driven History of Bioinformatics*. Chicago : University of Chicago Press.

Stevens, H. (2016). Hadooping the genome: The impact of big data tools on biology. *BioSocieties*, *11*(3), 352-371. https://doi.org/10.1057/s41292-016-0003-6

Thévenot, L. (2009). Postscript to the Special Issue: Governing Life by Standards: A View from Engagements. *Social Studies of Science*, *39*(5), 793-813. https://doi.org/10.1177/0306312709338767

Timmermans, S. (2015). Trust in standards: Transitioning clinical exome sequencing from bench to bedside. *Social Studies of Science*, *45*(1), 77-99. https://doi.org/10.1177/0306312714559323

Timmermans, S. & Almeling, R. (2009). Objectification, standardization, and commodification in health care: A conceptual readjustment. *Social Science & Medicine*, *69*(1), 21-27. https://doi.org/10.1016/j.socscimed.2009.04.020

Timmermans, S. & Berg, M. (1997). Standardization in Action: Achieving Local Universality through Medical Protocols. *Social Studies of Science*, *27*(2), 273-305. https://doi.org/10.1177/030631297027002003

Timmermans, S. & Berg, M. (2003). *The Gold Standard: The Challenge Of Evidence-Based Medicine*. Philadelphia, Pa : Temple University Press.

Timmermans, S. & Epstein, S. (2010). A World of Standards but not a Standard World: Toward a Sociology of Standards and Standardization. *Annual Review of Sociology*, *36*(1), 69-89. https://doi.org/10.1146/annurev.soc.012809.102629

Topol, E. (2019). *Deep Medicine: How Artificial Intelligence Can Make Healthcare Human Again*. New York, NY : Basic Books.

Turnbull, C., Scott, R. H., Thomas, E., Jones, L., Murugaesu, N., Pretty, F. B., Halai, D., Baple, E., Craig, C., Hamblin, A., Henderson, S., Patch, C., O'Neill, A., Devereau, A., Smith, K., Martin, A. R.,

Sosinsky, A., McDonagh, E. M., Sultana, R., … Caulfield, M. J. (2018). The 100 000 Genomes Project: bringing whole genome sequencing to the NHS. *BMJ*, *361*, k1687. https://doi.org/10.1136/bmj.k1687

Vinck, D., Camus, A., Jaton, F. & Oberhauser, P.-N. (2018). Localités distribuées, globalités localisées : Actions, actants et médiations au service de l'ethnographie du numérique. *Symposium*, *22*(1), 41-60.

Wagner, J., Olson, N. D., Harris, L., McDaniel, J., Cheng, H., Fungtammasan, A., Hwang, Y.-C., Gupta, R., Wenger, A. M., Rowell, W. J., Khan, Z. M., Farek, J., Zhu, Y., Pisupati, A., Mahmoud, M., Xiao, C., Yoo, B., Sahraeian, S. M. E., Miller, D. E., … Sedlazeck, F. J. (2022). Curated variation benchmarks for challenging medically relevant autosomal genes. *Nature Biotechnology*, *40*(5), 672-680. https://doi.org/10.1038/s41587-021-01158-1

Webster, A. & Eriksson, L. (2008). Governance-by-standards in the field of stem cells: managing uncertainty in the world of "basic innovation". *New Genetics and Society*, *27*(2), 99-111. https://doi.org/10.1080/14636770802077009

Willig, L. K., Petrikin, J. E., Smith, L. D., Saunders, C. J., Thiffault, I., Miller, N. A., Soden, S. E., Cakici, J. A., Herd, S. M., Twist, G., Noll, A., Creed, M., Alba, P. M., Carpenter, S. L., Clements, M. A., Fischer, R. T., Hays, J. A., Kilbride, H., McDonough, R. J., … Kingsmore, S. F. (2015). Whole-genome sequencing for identification of Mendelian disorders in critically ill infants: a retrospective analysis of diagnostic and clinical findings. *The Lancet Respiratory Medicine*, *3*(5), 377-387. https://doi.org/10.1016/S2213-2600(15)00139-3

Wu, B., Kang, W., Wang, Y., Zhuang, D., Chen, L., Li, L., Su, Y., Pan, X., Wei, Q., Tang, Z., Li, Y., Gao, J., Cheng, R., Zhou, W., Wang, Z., Qiu, G., Wang, J., Yang, L., Zhang, P., … Zhou, W. (2021). Application of Full-Spectrum Rapid Clinical Genome Sequencing Improves Diagnostic Rate and Clinical Outcomes in Critically Ill Infants in the China Neonatal Genomes Project*. *Critical Care Medicine*, *49*(10), 1674. https://doi.org/10.1097/CCM.0000000000005052

Yates, J. & Murphy, C. N. (2007, 1st january). Coordinating International Standards: The Formation of the ISO. *MIT Sloan Research Paper*. 4638-07 https://doi.org/10.2139/ssrn.962455

Zerubavel, E. (1982). The Standardization of Time: A Sociohistorical Perspective. *American Journal of Sociology*, *88*(1), 1-23. https://doi.org/10.1086/227631

Zook, J. M., Chapman, B., Wang, J., Mittelman, D., Hofmann, O., Hide, W. & Salit, M. (2014). Integrating human sequence data sets provides a resource of benchmark SNP and indel genotype calls. *Nature Biotechnology*, *32*(3), 246-251. https://doi.org/10.1038/nbt.2835

Zuboff, S. (2019). *The Age of Surveillance Capitalism: The Fight for a Human Future at the New Frontier of Power*. New York : PublicAffairs.

NOTES

1. I here agree with Peter Dear and Sheila Jasanoff when they write that what loosely connects the researchers in the heterogeneous field of STS is the conviction that "since the [work] of Ludwik Fleck, Thomas Kuhn, and David Bloor, [...] science is much more than the bloodless realm of logical empiricism and first principles, that people preexist their knowledge of the world (just as much as the world preexists the knowledges of people), that materiality matters in the making and proving of scientific truths, and that both the sciences and the dynamics of scientific and technological practice are fertile ground for social, political, and ethical analysis" (Dear & Jasanoff, 2010: 761).

2. On the frictional processes involved in defining standards, particularly IT ones, in scientific practices, see in Edwards *et al.* (2011) and Jaton & Vinck (2016).

3. As Busch sums it up well: "As standards are used, people and things are tested, and we determine what shall count. Those people and things that pass the tests or make the grade are drawn into various networks" (2013: 12).

4. As we shall see later, in this particular case study, accreditation is an official recognition, founded on a legal basis, attesting to compliance with an ISO standard. It differs from "simple" certification both in the type of trials it involves and in the opportunities it opens up.

5. The present inquiry derived from a project that explicitly set out to document the development of personalized medicine in Switzerland.

6. All personal and institutional names are fictitious, for reasons of confidentiality.

7. The International Organization for Standardization (ISO) is an independent institution headquartered in Geneva, Switzerland. Following the Second World War, ISO emerged as a key institution in the coordination of international standards. Once limited to manufactured products, ISO standards now extend to organizational practices, environmental management and human rights. On the still largely untold history of this institution, central to the great post-war acceleration, see Yates & Murphy (2007).

8. More specifically, QUALAB is an association made up of representatives from the Swiss Hospital Association, the Swiss Association of Analytical Laboratories, the Swiss Association of Healthcare Professionals, the Swiss Association of Pharmacists, the Swiss Association of Health Insurance Companies and the Swiss Medical Tariff Commission.

9. The list of analysis laboratories authorized by the FOPH is available here: https://backend.bag.admin.ch/fileservice/sdweb-docs-prod-bagadminch-files/files/2025/03/18/8b574501-5ab6-4d7f-8db0-5db05073db4d.pdf

10. Several private laboratories authorized by the FOPH and founded by former or current university professors also seem to benefit from this logic of geographical and institutional proximity.

11. Whole genome sequencing (WGS) defines all the nucleotides – base by base – in an individual's DNA, while whole exome sequencing (WES) focuses on the regions coding mainly for proteins (exons). In the specific case of the Center, RNA sequencing (RNAseq) was mainly used for the genetic study of viruses, in particular SARS-CoV-2.

12. FASTQ is the main text format used to store nucleotide sequences (e.g. "TTACCG") and a quality score for each nucleotide. In the case of sequencing devices distributed by Illumina – a major player in this market – FASTQ files are generally generated from data in Binary Base Call (BCL) format, in what is often referred to as "BCL-FASTQ conversion".

13. After generating the FASTQ data, which itself comes from raw sequenced data in BCL format, it is necessary to align them to a reference genome. The data resulting from this complex alignment process – often called "mapping" – are first encoded in a tab-delimited text format called Sequence Alignment/Map (SAM), then converted into a binary format – Binary Alignment/Map (BAM) – to facilitate further processing. However, due to the very large number of elements recorded in these BAM files, alignment errors are potentially numerous. Hence the need for more or less automated post-processing operations, which include, for example, removal or recalibration of base quality scores. Only once the BAM data have been post-processed can the variant calling analysis actually begin, leading to the generation of VCF (Variant Call Format) datasets that list what are often called "candidate variants." Most often, these lists of candidate variants encoded in VCF data are then refined – usually based on patients' phenotypes (when available) – to ultimately result in a list of "variants of interest." It is this list of variants of interest that, ideally, will be communicated in an Excel-type table to clinical geneticists to support certain diagnoses and therapeutic decisions. For more details on the (theoretical) process that allows the transition from FASTQ data to VCF data, see Pfeifer (2017).

14. GATK is the acronym for Genome Analysis Toolkit and constitutes a large modular set of programs for germline analysis. Originally published in 2010 by a small group of bioinformaticians from the Broad Institute of MIT and Harvard, it has since developed significantly to become the open-source industry gold standard for genetic variant calling.

15. DRAGEN was developed in the 2015s by the biotechnology startup Edico Genome. After its acquisition by Illumina in 2018 (for an undisclosed amount), DRAGEN was integrated into Illumina's sequencing portfolio.

16. Congenica is a digital health company based in the United Kingdom that markets an integrated software environment for the analysis, interpretation, and distribution of genomic data. Originating from Genomics England – the company owned by the UK Department of Health to carry out its 100,000 Genomes Project (Turnbull *et al.*, 2018) – Congenica has the advantage of being certified as a medical device (ISO 13485 standard) by the European Union, which makes the data it generates usable in most clinical contexts within the European Economic Area.

17. A shell script is a small computer program written in shell, a programming language designed to interact with the command-line interpreters of Unix-based operating systems such as Linux or macOS.

18. All the following figures are taken from a working .html document, written by Noah and Emily, which presents the procedure and results of their comparative experiment. All quotations are reconstructions based on notes hastily taken by the ethnographer.

19. For non-credited figures, we publish the data in agreement with the institution from which they originate. However, for reasons of confidentiality, we preserve the identity of the institution.

20. The quality score of GATK variants refers to the probability that the program correctly identifies a given position in the genome as a variation relative to the reference genome at at least one site. As explained on the GATK web page (GATK Team, 2024), this so-called Phred-scaled estimate (originally used to quantify the probability of base-calling errors in FASTQ data) can range from 0 to infinity. A higher score indicates a greater likelihood that a decision is correct, while a lower score suggests a higher probability that the decision is incorrect.

21. Genome in a Bottle refers to the authoritative human DNA standard established by the US-based National Institute of Standards and Technology from a blend of multiple individuals (Zook *et al.*, 2014). This reference standard is still being curated today, notably to better define its low complexity regions (Wagner *et al.*, 2022) and make it more capable of integrating human genetic diversity (Jarvis *et al.*, 2022).

22. IGV stands for Integrative Genomics Viewer, an open-source interactive genome visualization software developed and maintained by teams working at UC San Diego and the Broad Institute at MIT and Harvard. For more details on the history of IGV, see Robinson *et al.* (2011).

23. The numerous computational error correction techniques that are currently employed in genomics are often custom-based variations of well-known models (e.g., k-mer spectrum analysis). Most of them, however, require a decent variety of nucleotides in order to anchor their algorithmic operations. For a recent overview of errors correction techniques, see Mitchell *et al.* (2020).

24. A deletion ultimately represents a loss of genetic information – harmless if the deleted region is non-coding (as is the case in the vast majority of cases), but potentially pathogenic when it affects a critical region.

25. The Center was eager to promote this achievement, in line with its distinction strategy. In particular, this recognition was highlighted in a series of articles – some published by Illumina – which featured the Center as an ISO-accredited facility.

ABSTRACTS

For several decades, Science & Technology Studies (STS) have highlighted the central role of norms and standards in the construction and circulation of technoscientific and biomedical knowledge. However, two blind spots persist: on the one hand, the standardization of bioinformatics practices, essential in contemporary biomedicine, remains underexplored; on the other hand, preparations for standardization trials (tests, evaluations, audits) are rarely studied. This article partially fills these gaps by documenting the preparation for a standardization trial of a bioinformatics pipeline within a Swiss center specialized in computational genomics. Based on a four-month ethnographic study, it analyzes how a team of bioinformaticians compares two software suites – GATK and DRAGEN – for variant calling, as part of their efforts to meet the ISO 15189 standard for quality in biomedical laboratories. The study highlights the strategies implemented to identify, qualify, and negotiate discrepancies between these software tools, highlighting the room for interpretation inherent in bioinformatics standardization processes. The study also offers a broader reflection on the articulation between standardization and preparation in bioinformatics, suggesting that these trials are not limited to technical procedures but also involve creative work in optimization and anticipation. By revealing the dynamics of power, negotiation and adaptation that feed standardization practices in bioinformatics, this analysis contributes to a better understanding of the role of standards in the evolution of biomedical infrastructures that support the implementation of so-called personalized or precision medicine.

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Keywords: computational genomics, variant calling, standardization, precision medicine, personalized medicine, ethnography

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