Systematizing Genomic Privacy Research – A Critical Analysis

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Abstract

Rapid advances in human genomics are enabling life science researchers to gain a better understanding of the role of the variation in our ancestry, health, and well-being, which stimulates hope for more cost efficient and effective healthcare. However, this progress also yields a number of security and privacy concerns, stemming from the distinctive characteristics of genomic data. Aiming to address them, a new research community has emerged, producing a large number of publications and initiatives.

In this paper, we introduce and execute a structured methodology to systematize the current knowledge around genome privacy research, focusing on privacy-enhancing technologies used in the context of testing, storing, and sharing genomic data, while selecting a representative sample of the community's work. Using carefully crafted systematization criteria, we provide and discuss critical viewpoints and a comprehensive analysis on the timeliness and the relevance of the work produced by the community. In doing so, we highlight that proposed technologies can only offer protection in the short-term, scrutinizing assumptions made by the community, and analyzing the costs introduced by privacy defenses in terms of various types of utility and flexibility overhead.

1   Introduction

Facilitated by rapidly dropping costs, genomics researchers have made tremendous progress over the past few years toward mapping and studying the human genome. For instance, a number of genetic mutations have been linked to predisposition to various forms of diseases, including cancer [DGA10], as well as to response to certain treatments [ZBG+14]. Overall, this progress has stimulated hope for a new "precision medicine" era, where diagnosis and treatment can be tailored to individuals based on their genome, and thus enable more cost efficient, as well as effective, healthcare [Ash16]. Advances in genomics are already bearing fruit in clinical settings. With costs of whole genome sequencing now on the order of $1,000 and dropping [Hay14], clinicians can much more easily diagnose and/or treat patients affected by rare genetic disorders [BFG+17, GHKT+14].

The promise of improved healthcare has also encouraged ambitious initiatives to sequence large numbers of individuals, aiming to build biorepositories that will be made available for research purposes. In 2015, the US government announced the Precision Medicine Initiative (now known as the All Of Us Research Program [NIH17a]), which aims to collect health and genetic data from one million citizens. Similarly, Genomics England, a project funded by the UK government, aims to sequence the genomes of one hundred thousand patients focusing on rare diseases and cancer [Gen17]. Overall, the rise of data-driven genomics research prompts the need to facilitate data sharing. In recognition of this need, in 2013 the Global Alliance for Genomics and Health (GA4GH) was established with an objective to make data sharing between institutes simple and effective [ga417]. The GA4GH has developed various software, e.g., the Beacon Project [Bea17], allowing researchers to search if a certain allele exists in a database hosted at a certain organization (i.e., a Beacon), and the Matchmaker Exchange [PAB+15], which facilitates rare disease discovery.

At the same time, progress has also encouraged the rise of a flourishing private sector market. Several companies operate very successfully in the business of sequencing machines (e.g., Illumina), genomic data storage and processing (e.g., Google Genomics), or AI-powered diagnostics (e.g., Sophia Genetics). At the same time, others now offer genetic testing *directly* to their customers, without involving doctors or genetics experts in the process. There are now hundreds of direct-to-consumer (DTC) genetic testing companies [ISO17], with prominent examples including 23andMe and AncestryDNA, which have amassed several million customers [23a17, Anc17].

Privacy concerns. Alas, the widespread availability of genomic data also prompts ethical, security, and privacy concerns. Genomic data is challenging to anonymize [GMG+13, HSR+08, SB15] and contains information related a variety of factors, including ethnic heritage, disease predispositions, and many other phenotypic traits [FSC11]. Moreover, consequences of genomic data disclosure are not limited in time; mainly due to its hereditary nature, an adversary obtaining a target's genomic data can also infer a wide range of features that are relevant to her close relatives as well as her descendants. Therefore, since genomes do not change much over time and retain similarity across generations [HAHT13], disclosing the genomic data of a single individual might put at risk the privacy of others for a long period.

Some of these threats have already been demonstrated in practice. For instance, Homer et al. [HSR+08] show that one can determine whether a specific individual was part of a case study group associated to a certain disease by comparing their profile against the aggregate statistics about the case study to

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those of a reference population obtained from public sources. Also, Gymrek et al. [GMG+13] demonstrate how to infer the surnames of individuals from public anonymized genomic datasets (by profiling short tandem repeats on the Y chromosome while querying recreational genealogy databases).

Systematizing genome privacy research. Motivated by the need to reconcile privacy with progress in genomics, the research community has begun to investigate solutions for securely testing and studying the human genome. It is clear that privacy in genomics requires specific attention, due to the unique characteristics of the data. As a result, the "genome privacy" community has emerged, producing a relatively large number of publications on the topic, and several dedicated events, including international seminars [HHT14, HKMT16], the iDash competition series[1], or the GenoPri workshop.[2] At the same time, this community is partially operating ahead of the curve, proposing the use of privacy-enhancing technologies (PETs) in envisioned, rather than existing, settings. As discussed in this paper, genome privacy research often makes assumptions for the future; e.g., that cheap, error-free whole genome sequencing will soon be available to private citizens, and/or that individuals will be sequenced at birth so that all genetic tests can be easily and cheaply done via computer algorithms.

This prompts the timely need for a systematic analysis of genome privacy research, aiming to evaluate not only what the community has achieved so far, but also its outlook and the inherent challenges it faces. More specifically, we identify and address two main sets of research objectives in relation to the maturity and the relevance of genome privacy research:

(1) *Maturity:* By producing a critical, multi-faceted review of genome privacy research, we aim to assess whether or not proposed PETs are headed toward real-life deployment. If so, in what contexts? If not, why? What are the obstacles we need to overcome?

(2) *Relevance:* By systematizing knowledge around the problems and the solutions on which the community is working, we reason about their relevance, e.g., whether tools being proposed can respond to the needs of practitioners working on medical and research applications, and/or whether techniques involving consumers are compatible with the requirements of the market.

1.1 Roadmap

We set out to critically evaluate work produced by the genome privacy community across several axes, using a set of systematic criteria. These include the analysis of security and data representation assumptions, the protection against long-term threats, the overhead introduced by privacy protection, as well as the degradation in utility and flexibility of genomic data management and its processing.

Rather than attempting to present an exhaustive review of a very large number of papers on genome privacy, we adopt a methodology to systematically *sample* papers that are representative of privacy themes and solutions. Specifically, we focus on research relying on PETs in the context of testing, storing, and/or sharing genomic data. Hence, we retrieve the list of publications in the field from the community website GenomePrivacy.org while intentionally excluding attack papers and risk quantification efforts (see Section 3). After identifying relevant sub-areas of genome privacy research, we select results that provide a meaningful sample of the community's work in each area (see Section 4).

We then present a concise table (Table 1) and use it to summarize our systematization and to guide the detailed examination of a few key aspects of our effort (see Section 5). Finally, we discuss the genome privacy body of work as a whole, reflecting on its maturity and relevance (see Section 6).

Our systematization provides a novel viewpoint on the inherent challenges faced by genome privacy research, along with the difficulty of addressing some of them (e.g., the inadequate protection against long-term threats, the toll of protecting privacy on scalability, flexibility, and utility). Our analysis also questions some common assumptions about genomic data representation, as well as system and security models. Finally, our methodology can be relied upon in a few years to revisit new results as they become available, thus allowing us to quantify progress in genome privacy research.

1.2 SoK vs Survey/Position Papers

Over the past few years, several surveys and position papers have been published in the context of genome privacy. However, they neither fulfill our research objectives nor systematize and contextualize knowledge in this research field. Here, we provide a review of this papers to highlight the novelty and importance of this SoK.

Naveed et al.'s ACM Computing Surveys article [NAC+15] presents an overview of the genomic privacy field from a computer science perspective, reviewing known privacy threats, along with available solutions. They also discuss certain challenges (e.g., the existence of genomic databases not under the control of the health system, or that privacy protection often affects utility). In addition, they interview 61 experts in the biomedical field aiming to infer their concern (and knowledge) regarding genomics and privacy, finding that the majority of the respondents acknowledge the importance of genomic privacy research and risks from privacy breaches.

Unlike the previous paper, Akgün et al. [ABOS15] specifically focus on bioinformatics research where private information disclosure is possible (e.g., querying/searching genomic data, or sequence alignment, and survey available solutions for each of them). Dugan et al. [DZ16] review protocols that use Secure Multiparty Computation (MPC) as the main privacy defense mechanism in the context of genomic testing. They group methods into four categories based on the cryptographic tools and compare their performance and se-

curity. Furthermore, Shi et al. [SW17] describe the current state of genomic data sharing, the potential privacy risks, as well as regulatory and ethical challenges. They also categorize tools for protecting privacy as controlled access, data perturbation (specifically in the context of differential privacy), and cryptographic solutions, providing an overview for each category. Ayday et al. [ADHT15] summarize the importance of progress in genomics along with the need for preserving the privacy of the users when dealing with their genomic information. Also, Wang et al. [WJS⁺17] study the clinical, technical, and ethical sides of genomic privacy in the United States, describing available privacy-preserving solutions for the disclosure of results from genomic studies as well as for record linkage, along with the ethical and legal implications of genomic privacy in conjunction to informed consent.

Overall, these surveys and position papers are limited to reviewing and summarizing available solutions. Combined together, they are useful in providing an overview of the state of the art, as well as the different avenues for privacy protection, highlighting challenges from non-technical perspectives, including ethics, law, and regulation. By contrast, our work introduces and executes a methodology, which, along with our systematization criteria, helps us *evaluate* the field as a whole, via representative work, and provide a *critical* analysis of the community's directions, challenges, and outlooks.

2   Genomics Primer

An important milestone in genomics was the completion, in 2003, of the Human Genome Project, an ambitious international effort started in 1990 to sequence and map all the genes in the human genome [Nat17a]. Early whole genome sequencing (WGS) technologies, based on microarrays, were quite slow and costly; then, in 2007, DNA sequencers became available that worked at a lower cost, and faster, with the help of powerful computers geared to reassembling multitudes of smaller DNA segments. WGS costs are now on the order of $1,000 and continue to decrease [Nat17b].

Sequencing is not the only way to analyze the genome; in fact, in-vitro techniques such as *genotyping* are routinely used to look for known genetic differences using biomarkers. However, scientists hope that affordable WGS will help them understand how the genome as a whole works, as well as advance knowledge and treatment of rare genetic disorders. It also allows them to sequence large numbers of genomes and study the relationship between genetic features (e.g., predisposition to diseases and response to treatments). This progress is also fostering the emerging DTC market, with companies offering genetic testing for a few hundred US dollars or less. Customers provide a biospecimen (e.g., saliva) sample via mail and, a few days later, are given access to reports related to health (e.g., susceptibility to Parkinson's disease), carrier status, wellness (i.e., how well they metabolize caffeine), and ancestry.

SNPs, CNVs, STRs, and RFLPs. All members of the human population shares around 99.5% of the genome, with the remaining 0.5% differing due to genetic variations. Single Nucleotide Polymorphisms (SNPs) are the most common type of variation [NIH17b]. A SNP is a variation at a single position, occurring in 1% or more of a population. SNPs constitute the most commonly studied genetic feature today, as researchers use them to identify clinical conditions, predict the individuals' response to certain drugs, and their susceptibility to various diseases [WMM⁺13]. However, Copy Number Variations (CNVs) [SFD⁺07] and Short Tandem Repeats (STRs) [B⁺07] are also becoming increasingly more used. In this paper, we also refer to Restriction Fragment Length Polymorphisms (RFLPs), which refer to the difference between samples of homologous DNA molecules from differing locations of restriction enzyme sites, and are used to separate DNA into pieces and obtain information about the length of the subsequences.

FSGs. WGS is the process of determining the complete DNA sequence of an organism's genome. In other words, it is used to digitize the genome of an individual into a series of letters corresponding to the various nucleotides (A, C, G, T). Fully Sequenced Genomes (FGSs) are typically stored in either SAM, BAM, or FASTQ formats. SAM (Sequence Alignment Map) is a text-based format, which may include additional information such as the reference sequence of the alignment or the mapping quality, BAM is a binary format (in practice, the compressed and lossless version of SAM), while FASTQ is another text-based format which stores nucleotide sequences along with their corresponding quality scores.

GWAS. Finally, important progress is also being made with Genome-Wide Association Studies (GWAS), which aim to discover whether a genetic variant is associated with some trait. GWAS compare the DNA of study participants to discover SNPs that occur more frequently in people carrying a particular disease, and help researchers better understand diseases.

3   Methodology

In this section, we present the methodology used for our systematization. First, we discuss how we select relevant work in genome privacy, aiming to choose a representative sample from the community's work. Then we present the criteria used to systematize knowledge.

3.1   Sampling Genome Privacy Research

Genomeprivacy.org publication list. As we aim to study research on genome privacy from a privacy-enhancing technologies (PETs) point of view, we focus on work using PETs in the context of testing, storing, and/or sharing genomic data. Hence, we rely on the website GenomePrivacy.org, or "the community website for sharing information about research on the technical protection of genome privacy and security" as it promotes itself.

In Summer 2017, we retrieved the *197 articles* listed on the site, most of which are published in computer science venues,

with a few articles appearing in bioinformatics journals. We group them into several canonical categories – Personal Genomic Testing, Genetic Relatedness Testing, Access and Storage Control, Genomic Data Sharing, Outsourcing, and Statistical Research – and proceed to select a sample that can meaningfully represent the state of the art for each category.

Excluding attack papers. Note that we exclude work on attacks [BBHM16, Goo09, GMG+13, HSR+08, SB15], as well as privacy quantification [HAHT13, HAHT14], as our main focus is on the use of PETs in the context of genomics. A thorough overview of techniques that can be used to violate genomic privacy is presented in [EN14]. We also refer readers to [Wag15] for a comprehensive evaluation of metrics geared to quantify genomic privacy, and to [WVX+17] for game-theoretic approaches to quantifiable protection in genomic data sharing. We do not include recent proposals to address specific attacks in the context of the Beacon Network [SB15] either, such as, the work by Raisaro et al. [RTJ+17] or Wan et al. [WVKM17], although we discuss them later in Section 6.

Final selection. In order to select a final list of papers to be reviewed (Section 4) and used to drive our systematization effort (Section 5), we follow an *iterative* process. First, we select **45 articles** (out of the 197 papers identified above) we believe are representative of the state of the art of all of the six categories. Then, since it would be impossible to review and systematize all of them in a succinct and seamless manner, we trim the selection down to **21 papers**. When deciding whether to include one paper over another, we tend to prefer papers published in venues that are more visible to the privacy-enhancing technologies community or that have been cited significantly more, as they might arguably have a stronger influence on the community in the coming years.

Ultimately, the selection covers Personal Genomic Testing (5 papers), Genetic Relatedness Testing (3), Access & Storage Control (4), Genomic Data Sharing (4), Outsourcing (4), and Statistical Research (3). Note that two articles appear in both Personal Genomic Testing and Genetic Relatedness Testing categories. For completeness, in Section 4, we also add a citation to the papers from the first list of 45 papers that are not included in the final selection.

Remarks. Our effort does *not* aim to analyze all papers related to genomic privacy. Rather, we focus on the use of privacy-enhancing technologies and contributions from the genome privacy community (thus choosing GenomePrivacy.org as our main source). We aim to systematize knowledge and critically evaluate privacy defense mechanisms. Thus, our selection is meant to be representative of the state of the art for each of the identified category, but not of its breadth or depth. As a consequence, *even if one added or replaced one paper with another, our main takeaways would not be considerably altered.*

3.2 Systematization Criteria

We now discuss the main axes along which we systematize genome privacy work, aiming to support a critical analysis of trends, challenges, and opportunities. More specifically, we elicit a set of criteria with the goal of helping ourselves answer the questions set in Section 1. To this end, we define the systematization criteria that allow for a comprehensive evaluation of the genome privacy papers. These criteria constitute the columns of Table 1 (see Section 5), where each row is one of the papers discussed below. Basically, we include a criterion if it helps achieve our research objectives set out earlier.

Overview. We start by noting the type of genomic data each solution operates on (e.g., fully sequenced genomes or SNPs) and in what format. We also analyze whether or not techniques make assumptions with respect to custom/simplified formats or the lack of (sequencing) errors, aiming to later capture issues challenging real-world deployment. We also track where the data is stored, as this plays a crucial role for both security and usability. Next, we consider what kind of third-party entities are used, and whether they come with non-collusion or other security assumptions. Finally, we consider the underlying tools used to protect privacy, and how these may affect efficiency and utility. The nine selected criteria are detailed below.

1. Data Type. We capture the type of genomic data used; e.g., some protocols perform computation on full genomes, or other aspects of the genome (e.g., SNPs and haplotypes).

2. Genomic Assumptions. We elicit whether techniques make any assumptions as to the *nature* of the data. For instance, the processing of sequencing data is not perfect and certain letters (or even sequences of letters) might be misreported or deleted, while others might be inserted unexpectedly. In fact, the error rate percentage across various next-generations sequencers can be as high as 15% [GMM16]. For this reason, the output of modern Illumina sequencing machines (i.e., FASTQ format [Ill17]) is made of segments of DNA with probabilities associated with the confidence that letters were read correctly. This criterion serves as a method for noting which of the proposed methodologies take into consideration, or are particularly affected by this.

3. Locale of Genomic Data. We study where genomic data is assumed to be stored, e.g., on a personal device like a mobile phone or a dedicated piece of hardware, or in the cloud. Data here pertains to either individuals' genomes, or to datasets collected/belonging to institutions (e.g., biobanks and hospitals), which we refer to as Data Owners.

4. Use of Third Parties. We determine the presence of third parties, if any, as well as their nature. For instance, some protocols may involve Key Distribution Centers and semi-trusted cloud storage providers.

5. Long-Term Security. Due to its hereditary nature, the sensitivity of genomic data does not degrade quickly over the years: even access to the genome of a long-deceased individual might still pose a threat to their descendants. Therefore, we look at the underlying building blocks and the com-

putational assumptions in genome privacy tools and analyze whether or not they can realistically withstand several decades.

6. Security Assumptions. We analyze the threat model under which each solution operates, e.g., if they assume semi-honest or fully malicious adversaries. We also study assumptions made on entities involved, for instance, whether third parties are assumed not to collude with any other entities.

7. Tools. We also report the main security tools used, e.g., secure multiparty computation, homomorphic encryption, etc.

8. Privacy Overhead. We attempt to quantify the overhead introduced by the privacy defense mechanisms, compared, whenever possible, to non privacy-preserving versions of the same functionality. This is a non-trivial task since each sub-area of genome privacy has different goals and each piece of work in that area does not necessarily solve the exact same problem. Nonetheless, we analyze computational complexity of each solution, as well as bandwidth and storage consumption, aiming to broadly assess their efficiency. We also take into account the overall scalability of the system, which we defined as either low or high, as discussed in Section 5.

9. Utility Loss. Finally, we measure the impact of privacy tools on the overall utility of the system. Such measurements include the overall flexibility of the proposed work in comparison with the intended task. Similar to the above criteria, we compare against non-privacy-preserving versions of the same functionality, and grossly quantify utility loss as either low or high.

4 Representative Work

We now review the research on genome privacy selected following the methodology presented in Section 3. The papers we select constitute the rows presented later in Table 1 and are cited in a different color, using [AuthYY].

4.1 Personal Genomic Testing

We start by focusing on work realizing privacy-preserving versions of personal genomic tests. These have a variety of uses, including aiming to assess a person's predisposition to a disease, determine the best course of treatment, or optimize drug dosage. Typically, they involve an individual and a testing facility, and consist of searching for and weighting either short patterns or SNPs (cf. Section 2). In this context, there are two main privacy-friendly models: (1) one assuming that individuals keep a copy of their genomic data and consent to tests so that only the outcome is disclosed and (2) another involving a semi-trusted party that stores an encrypted copy of the patient's genetic information, and is involved in the interactions.

Baldi et al. [BBD+11] operate in model (1), supporting privacy-preserving searching of mutations in specific genes. They use authorized private set intersection (APSI) [DT10], which guarantees that the test is authorized by a regulator ("authorization authority") and pushes pre-computation offline so that the complexity of the online interaction only de-

pends on the handful of SNPs tested. It also ensures that the variants which make up the test are kept confidential, as this may pertain to a company's intellectual property.

Ayday et al. [ARHR13] introduce (2), letting a Medical Center (MC) perform private disease susceptibility tests on patients' SNPs, by computing a weighted average of risk factors and SNP expressions. Patients have their genome sequenced once, through a Certified Institution (CI) which encrypts the SNPs and their positions, and uploads them to a semi-trusted Storage and Processing Unit (SPU). The MC computes the disease susceptibility using cryptographic tools, such as homomorphic encryption and proxy re-encryption. Also in model (2) is the work by Naveed et al. [NAP+14], whereby the CI encrypts genomes using controlled-functional encryption (C-FE), under a public key issued by a central authority, and publishes the ciphertexts. MCs can then run tests using a one-time function key, obtained by the authority, which corresponds to one specific test and can only be used for that test.

Djatmiko et al. [DFB+14] operate in both models (i.e., patients control their data by storing it on a personal device or in the cloud) to support personalized drug dosing (which in this case happens to be Warfarin, a blood thinner). The testing facility retrieves data to be evaluated (using private information retrieval [CGKS95]) and processes it while encrypted. The patient then securely computes the linear combination of test weights (using additively homomorphic encryption), and shows the results to the physician. Finally, Humbert et al. [HAHT14] consider the case of individuals willing to donate their genomes to research. They quantify the privacy risk for an individual using a "global privacy weight" of their SNPs and use an obfuscation mechanism that functions by hiding SNPs.

Personal Genomic Testing – Selection

1. Baldi et al., CCS'11 [BBD+11]
2. Ayday et al., WPES'13 [ARHR13]
3. Naveed et al., CCS'14 [NAP+14]
4. Djatmiko et al., WPES'14 [DFB+14]
5. Humbert et al., WPES'14 [HAHT14]

Other Work

See [TPKC07], [BA10], [DFT13], [SNR16], [MRA+16]

4.2 Genetic Relatedness

We next look at genetic relatedness, i.e., testing aimed to ascertain genealogy or ancestry of individuals. Genealogy tests determine whether two individuals are related (e.g., father and child) or to what degree (e.g., they are n^{th} cousins), while, ancestry tests estimate an individual's genetic "pool" (i.e., where their ancestors come from). These tests are often referred to as part of "recreational genomics", and are one of the drivers of the DTC market (with 23andMe and AncestryDNA offering them at under $100). Privacy research in this area aims to support privacy-respective versions of such tests.

Baldi et al. [BBD+11] allow two users, each holding a copy of their genome, to simulate *in vitro* paternity tests based on RFLPs, in such a way that they do not have to disclose their genomes to each other or third-parties, using private set intersection protocols [DGT12]. He et al. [HFH+14] let individuals privately discover their genetic relatives by comparing their genomes to others stored, encrypted, in the same biorepository, using fuzzy encryption [DRS04] and a novel secure genome sketch primitive, which is used to encrypt genomes using a key derived from the genome itself. Finally, Naveed et al. [NAP+14] rely on C-FE to enable a client to learn certain functions, including paternity and kinship, over encrypted data, using keys obtained from a trusted authority.

It should be recognized that the tools above differ in a few aspects. First, [BBD+11] assumes individuals obtain and store a copy of their sequenced genome, whereas [HFH+14] and [NAP+14] operate under the assumption that the users will rely on cloud providers. Second, [BBD+11] operates on full genomes, while [NAP+14] supports SNP profiles obtained from DTC genomics companies, with [HFH+14] requiring individuals' haplotypes.

Genetic Relatdness – Selection

1. Baldi et al., CCS'11 [BBD+11]
2. He et al., Genome Research'14 [HFH+14]
3. Naveed et al., CCS'14 [NAP+14]

Other Work

[HJW+14], [DCLZ16], [MRA+16]

4.3 Access and Storage Control

Next, we discuss key results broadly aiming to guarantee secure access to, and storage of, genomic data.

Karvelas et al. [KPK+14] use a special randomized data structure based on Oblivious RAM (ORAM) [GO96] to store data while concealing access patterns, using two servers to cooperatively operate the ORAM. Clients can then query data using a third entity who retrieves encrypted data from the ORAM and instructs the servers to jointly compute functions using secure two-party computation [Yao86]. Ayday et al. [ARH+14] present a framework for privately storing, retrieving, and processing SAM files. As in their previous work [ARHR13], a CI sequences and encrypts patients' genomes, and also creates the SAM files, storing them encrypted in biorepositories. Then MCs, using order-preserving encryption [AKSX04], can then retrieve data and conduct genetic tests.

Beyond SAM files, genomic data is also stored in BAM (a binary version of SAM) or CRAM files, which allows a lossless compression. Huang et al. [HAL+16] introduce a Secure CRAM (SECRAM) format, supporting compression, encryption, and selective data retrieval. SECRAM requires less storage space than BAM, and maintains CRAM's efficient compression and downstream data processing. Finally, Huang et al. [HAF+15] focus on long-term security, introducing the GenoGuard system, which aims to protect encrypted

genomic data against an adversary who tries to brute-force the decryption key (likely to succeed in 30 years). They specifically rely on Honey Encryption (HE) [JR14] so that, for any decryption attempt using an incorrect key, a random yet plausible genome sequence is produced.

Overall, we find that security issues in this context are not explored in as much depth as other areas.

Access and Storage Control – Selection

1. Karvelas et al., WPES'14 [KPK+14]
2. Ayday et al., DPM'14 [ARH+14]
3. Huang et al., IEEE S&P'15 [HAF+15]
4. Huang et al., Genome Research'16 [HAL+16]

Other Work

[TPKC07], [KJLM08], [BA10], [CKM12]

4.4 Genomic Data Sharing

We now discuss results in the context of genomic data sharing, which is unsurprisingly an important aspect of for hypothesis-driven research. Consider, for instance, GWAS: in order to elicit robust conclusions on the association between genomic features and diseaseas and traits, researchers may need millions of samples [BHF+08]. Even if sequencing costs continue to rapidly drop, it is unrealistic to assume that research teams can easily gain access to such a large number of records. Yet, though there is an interest in data sharing, these sharing initiatives face several obstacles, as (1) researchers in isolation may be prevented from (or are hesitant to) releasing data, and (2) might only have patients' consent for specific studies at specific institutions. Therefore, privacy-enhancing methods have been proposed to address these issues.

Kamm et al. [KBLV13] present a data collection system where genomic data is distributed among several entities using secret sharing. MPC is then used to conduct computations on the data, privately, supporting secure GWAS across multiple entities, such as hospitals and biobanks. Xie et al. [XKB+14] introduce SecureMA, which allows secure meta-analysis for GWAS. (Meta-analysis is a statistical technique to synthesize information from multiple independent studies [EI13].) Their framework generates and distributes encryption/decryption keys to participating entities, encrypts association statistics of each study locally, and securely computes the meta-analysis results over encrypted data.

Wang et al. [WHZ+15] enable clinicians to privately find similar patients in biorepositories, e.g., to find out how these patients respond to certain therapies. In this investigation, similarity is defined as the edit distance, i.e., the minimum number of edits needed to change one string into another. Using optimized garbled circuits, [WHZ+15] they build a genome-wide, privacy-preserving similar patient query system. It should be noted that this protocol requires participating parties (e.g., medical centers) to agree on a public reference genome and independently compress their local genomes using a reference genome, creating a Variation Call

Format (VCF) file. The edit distance of two genomes can then be calculated by securely comparing the two VCF files. Finally, Chen et al. [CWJ+17] introduce a framework for private computations, including association studies for rare diseases (e.g., the Kawasaki Disease [KDB+11]), over encrypted genomic data of different jurisdictions. They rely on Intel's Software Guard Extensions (SGX), which provides a way of isolating sensitive data in a protected enclave and then securely computing the results [AGJS13].

In summary, work in this category focus on a wide range of problems, from GWAS and meta-analysis to edit distance computation. Also, tools primarily build on cryptographic protocols, except for [CWJ+17], which relies on SGX.

Genomic Data Sharing – Selection

1. Kamm et al., Bioinformatics'13 [KBLV13]
2. Xie et al., Bioinformatics'14 [XKB+14]
3. Wang et al., CCS'15 [WHZ+15]
4. Chen et al., Bioinformatics'17 [CWJ+17]

Other Work

[SST+14], [ZBA15], [AMH+16], [WZD+16], [WVX+17]

4.5 Outsourcing

At times, research and medical institutions often lack the computational resources required to store and/or process large genomic datasets locally, such that there is increasing interest in outsourcing data computation to the cloud, e.g., using dedicated services like Google Genomics or Microsoft Genomics. However, this introduces the need to trust cloud providers, which raises security and privacy concerns with respect to data of research volunteers and/or patients.

To address these concerns, several solutions have been proposed that rely on homomorphic encryption to let cloud providers perform genomic computations, privately, over encrypted data. Yasuda et al. [YSK+13] present a somewhat homomorphic encryption scheme (SWHE) for secure pattern matching using Hamming distance. More specifically, in this setting physicians supply patients with homomorphic encryption keys who then encrypt their genomic data and upload them to the cloud. When the physician needs to test whether a certain DNA sequence pattern appears in the patient's genome, the cloud computes the Hamming distance over encrypted DNA sequences and the desired pattern, and sends the (encrypted) result back to the physician. Cheon et al. [CKL15] also use SWHE to calculate the edit distance of two encrypted DNA sequences, allowing data owners (e.g., patients) to encrypt their genomic data and upload them to the cloud, which can calculate the edit distance to the reference genome or other encrypted sequences.

Lauter et al. [LLAN14] introduce a leveled homomorphic encryption scheme (LHE) to securely process genomic data in the cloud for various genomic algorithms used in GWAS, such as Pearson Goodness-of-Fit and χ^2-statistics tests. (LHE is a fully homomorphic encryption scheme variant that does not require bootstrapping but can evaluate cir-

cuits with a bounded depth.) Usually, computation of these statistics require frequencies or counts but, since their scheme cannot perform homomorphic divisions, [LLAN14] have to modify some of these computations to work with counts only. Finally, Kim et al. [KL15] also use SWHE to securely compute minor allele frequencies and χ^2-statistics for GWAS-like applications, over encrypted data, as well as the Edit/Hamming distance over encrypted genomic data.

Overall, the solutions discussed above, although focusing on different problems, are similar in that they all use variants of homomorphic encryption to securely compute over encrypted genomes.

Outsourcing – Selection

1. Yasuda et al., CCSW'13 [YSK+13]
2. Lauter et al., LatinCrypt'14 [LLAN14]
3. Cheon et al., FC'15 [CKL15]
4. Kim et al., BMC'15 [KL15]

Other Work

[CPWT12], [BLN14], [XKW+14], [ZDJ+15], [GAM+16]

4.6 Statistical Research

Our last category focuses on attempts to address unintended leakage threats from the disclosure of genomic data statistics. Recall that attacks have already been demonstrated, which for example, determine the presence of an individual in a case-study group (e.g., users with a certain disease) from Homer's attack on aggregate allele frequencies [HSR+08, DSS+15], or from correlation statistics of a few hundreds of SNPs [WLW+09]. Prior work has also shown that it is possible to reveal whether a person has participated in a GWAS, using regression coefficients [IGNC12], or to perform membership inference against individuals contributing microRNA expressions to scientific studies [BBHM16].

One possible defense against these attacks is through statistical disclosure control, of which differential privacy (DP) is one related approach. Specifically, DP allows to define private functions that are free from such inferences, providing as accurate query results as possible, while minimizing the chances for an adversary to identify the contents of a statistical database [DMNS06].

Johnson and Shmatikov [JS13] point out that it is inherently challenging to use DP techniques for GWAS, since these methods tend to output correlations between SNPs and the number of outputs is far greater than that of the inputs (i.e., the number of participants). In theory, it is possible to limit the number of available outputs and provide results with adequate accuracy [BLST10, FSU11]. In practice, however, this requires researchers to know beforehand what to ask (such as the top-k most significant SNPs), which is often infeasible, since, finding all statistically significant SNPs is often the goal of the study. Aiming to address this issue, [JS13] defines a function based on the exponential mechanism which is responsible for adding noise and works for arbitrary outputs. Using this mechanism, they let researchers perform ex-

ploratory analysis, including computing: i) the number and location of the most significant SNPs to a disease, ii) the p-values of a statistical test between a SNP and a disease, iii) any correlation between two SNPs, and iv) the block structure of correlated SNPs, in a differentially private way.

Uhlerop et al. [USF13] aim to address Homer's attack [HSR+08] using a differentially private release of aggregate GWAS data, supporting a computation of differentially private χ^2-statistics and p-values, and provide a DP algorithm for releasing these statistics for the most relevant SNPs. They also support the release of averaged minor allele frequencies (MAFs) for the cases and for the controls in GWAS. Then, Tramèr et al. [THHA15] build on the notion of Positive Membership Privacy [LQS+13] and introduce a weaker adversarial model, also known as Relaxed DP, in order to achieve better utility by identifying the most appropriate adversarial setting and bounding the adversary's knowledge.

Statistical Research – Selection

1. Johnson and Shmatikov, KDD'13 [JS13]
2. Uhlerop et al., JPC'13 [USF13]
3. Tramèr et al., CCS'15 [THHA15]

Although we do not include papers on statistical research in Table 1 as most criteria are not applicable to them, we discuss them in Section 5.4.

Other Work

[YFSU14], [ZWJ+14], [JZW+14], [WZD+16], [SB16],

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5 Systematization

In this section, we present a critical analysis of genome privacy research as it stands today, building on the methodology and the research results discussed in Section 3 and 4, respectively.

We drive our discussion from Table 1, which, besides providing a birds-eye overview of the community's work, also concisely summarizes the results of our systematization effort and allows us to discuss insights, research gaps, as well as challenges to certain assumptions.

5.1 The Issue with Long-Term Security

The longevity of security and privacy threats stemming from the disclosure of genomic data is substantial for several notable reasons. First, access to an individual's genome allows an adversary to deduce a range of genomic features that may also be relevant for her descendants, possibly several generations down the line. Thus, the sensitivity of the data does not necessarily degrade quickly, even after its owner has deceased. Moreover, the full extent of the inferences one can make from genomic data is still not clear, as researchers are still studying and discovering the relationship between genetic mutations and various phenomena.

These issues also imply that the threat model under which a volunteer decides to donate their genome to science, or have it tested by a DTC company, is likely to change in the future. As a consequence, the need or desire to conceal one's

genetic data might evolve. For instance, a family member may decide to enter politics, or a country's political landscape shifts toward supporting racist ideologies aimed to discriminate against or exclude members of a certain ancestral heritage.

Inadequacy of standard cryptographic tools. We find that the vast majority of genome privacy solutions rely on cryptographic tools, yet, they are not fit for the anticipated purpose if long-term security is to be protected. Recall that modern cryptosystems assume that the adversary is computationally bounded, as per a security parameter.[3] Suggestions for appropriate choices of the value for this parameter, and resulting key sizes, are regularly updated by the cryptography community, however, assuming at most the need for security for thirty to fifty years [SRG+14]. While this timeframe is more than adequate in most cases (e.g., classified documents get regularly de-classified, financial transactions/records become irrelevant, etc.), it may not be in the case of genomic data.

In theory, one could increase key lengths indefinitely, but, in practice, this is not possible for all cryptosystems. For instance, the block and stream ciphers available today are only designed to work with keys up to a certain length, while cryptographic libraries implementing public-key cryptography also impose a limit on key sizes. Furthermore, flaws in cryptosystems considered secure today may be discovered (as happened, recently, with RC4 or SHA-1), and quantum computing might eventually become a reality [Lan17].

What it means. Naturally, the issue of long-term security affects different genome privacy solutions in different ways. For instance, if genomic information is stored in an encrypted form and processed by a specialized third entity, such as the SPU in [ARHR13], then a malicious or compromised entity likely has multiple chances over time to siphon encrypted data off and succeed in decrypting it in the future.

This is also the case in settings where biobanks store patients' encrypted SAM files [ARH+14] or in the context of secure outsourcing solutions, where genomic information is offloaded and encrypted, to a cloud provider. On the other hand, if encrypted data is only exchanged when running cryptographic protocols, but not stored long-term elsewhere (as in [BBD+11, DFB+14, XKB+14]), then the adversary has a more difficult task. Nonetheless, long-term security compromise is still possible, even by an eavesdropping adversary and even if the protocol run is super-encrypted using TLS. (In fact, documents leaked by Edward Snowden revealed that the NSA has tapped submarine Internet cables and kept copies of encrypted traffic [Mar13, Bra14].)

Possible countermeasures. Our analysis indicates that the genome privacy literature has not sufficiently dealt with long term security. In fact, only the work by Huang et al. [HAF+15] attempts to do so, relying on Honey Encryption to encrypt and store genomic data. Although we believe

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[3]Given a security parameter λ, the adversary can only break the cryptosystem, with non-negligible probability, in time exponential in λ, but can run for time super-polynomial in λ.

	Data	Genomic Assumptions	Locale	Long-Term Security	Third Parties	Security Assumptions	Tools	Privacy Overhead	Utility Loss
Personal Genomic Testing									
[BBD+11]	FSG	Yes	User	No	AA	SH, NC	A-PSI	High	Low
[ARHR13]	SNP	No	Cloud	No	SPU	SH, NC	Pallier, Proxy	High	Low
[DFB+14]	SNP	No	User/Cloud	No	N/CS	SH	Pallier, PIR	Low	Low
[NAP+14]	SNP	No	Cloud	No	CA, CS	SH, NC	C-FE	Low	Low
[HAHT14]	SNP	No	Cloud	No	No	SH	DataSuppr	Low	Low
Genetic Relatedness Testing									
[BBD+11]	FSG	Yes	User	No	No	SH	PSI-CA	Low	High
[HFH+14]	Hapl	No	Cloud	No	CS	SH	Fuzzy	Low	Low
[NAP+14]	SNP	No	Cloud	No	CA, CS	SH, NC	C-FE	Low	Low
Access & Storage Control									
[KPK+14]	FSG	No	Cloud	No	CS	SH, NC	ElGamal, ORAM	High	Low
[ARH+14]	FSG	No	Cloud	No	CS, MK	SH, NC	OPE	High	Low
[HAF+15]	FSG	Yes	Cloud	Yes	CS	SH	HoneyEncr	High	High
[HAL+16]	FSG	No	User/Cloud	No	No	SH	OPE	Low	Low
Genomic Data Sharing									
[KBLV13]	SNP	No	Cloud	Yes	CS	SH, NC	SecretSharing	High	High
[XKB+14]	SNP	No	DataOwner	No	KDC	SH, NC	Pallier, MPC	High	High
[WHZ+15]	VCF	No	DataOwner	No	No	SH	MPC	High	Low
[CWJ+17]	SNP	No	DataOwner	No	No	SGX	SGX	Low	High
Outsourcing									
[YSK+13]	FSG	No	Cloud	No	CS	SH	SWHE	High	Low
[LLAN14]	SNP	No	Cloud	No	CS	SH	LHE	High	High
[CKL15]	FSG	No	Cloud	No	CS	SH	SWHE	High	High
[KL15]	FSG	No	Cloud	No	CS	SH	SWHE	High	Low

Third Parties: CS: Cloud Storage, SPU: Storage & Processing Unit, AA: Authorization Authority, CA: Central Authority, KDC: Key Distribution Center, MK: Masking & Key Manager, No: No Third Party

Data: FSG: Fully Sequenced Genome, SNP: SNPs, Hap: Haplotypes, VCF: Variation Call Format

Tools: SWHE: Somewhat Homomorphic Encryption, LHE: Leveled Homomorphic Encryption, Fuzzy: Fuzzy Encryption, PSI-CA: Private Set Intersection Cardinality, A-PSI: Authorized Private Set Intersection, C-FE: Controlled Functional Encryption, HoneyEncr: Honey Encryption, OPE: Order-Preserving Encryption, MPC: Secure Multiparty Computation, SGX: Software Guard Extensions

Security Assumptions: SH: Semi-Honest, M: Malicious, NC: No Collusions, SGX: Software Guard Extensions

Table 1: A systematic comparison of the representative genomic privacy methodologies. The rows represent each work and the columns represent the list of criteria we apply for assessment purposes.

this a step in the right direction, this technique only serves as a storage mechanism. It is not compatible with solutions supporting selective retrieval of genomic information, testing over encrypted data, and data sharing. Moreover, as discussed in Section 5.2, it has several important security limitations.

Cryptosystems providing information theoretic security could in theory help, as they are secure even when the adversary has unlimited computing power. Unfortunately, these require keys as long as the plaintexts and do not support the homomorphic properties that are needed to perform typical requirements for genomic data (e.g., testing or sharing). Work relying on secret sharing [KBLV13] is somewhat of an exception, in that it provides information theoretic guarantees. However, for secret sharing to work, one needs a collection of non-colluding entities, which is a requirement that is not always easy to attain.

Take-Away 1. The issue of long-term security has been neglected by the majority of genome privacy solutions and, even when addressed, it has been done so inadequately.

5.2 Security Limitations

As can be seen in Table 1, genome privacy protocols make a number of security assumptions that require further discussion.

Semi-honest adversaries. The majority of genome privacy solutions consider only semi-honest security, with rare exceptions represented by possible extensions to [BER$^+$15, BBD$^+$11]. Arguably, this may be due to the fact that solutions in this model are significantly easier to instantiate and yield computation and communication complexities that are often orders of magnitude lower than in the malicious model. We believe this is particularly salient in the context of genomics. However, security in semi-honest settings assumes that the parties do not deviate from the protocol and fails to guarantee correctness (i.e., a corrupted party cannot cause the output to be incorrectly distributed) or input independence (i.e., that an adversary cannot make its input depend on the other party's input) [HL10]. Moreover, in the semi-honest model, parties are assumed to not alter their input.

In practice, these requirements impose important limitations on the real-world security offered by genome privacy solutions. Specifically, it might not suffice to ensure that protocols only disclose the outcome of a test to a testing facility or provide hospitals with only information about common/similar patients. Indeed, this makes no guarantees as to whether the contents of the test or the patient information has not been maliciously altered or inflated. Additionally, the privacy layer makes it more difficult and, at times, impossible, to verify the veracity of the inputs. There are only several exceptions which consider the need for input authorization [BBD$^+$11, NAP$^+$14], but ultimately it is not always possible to identify an authority that can viably do so. Moreover, at the moment, present protocols that include authorization only work in very specific settings.

Non-Collusion. We also observe that a number of solutions that involve third parties (e.g., for storage and processing encrypted genomic data [ARHR13], issuing keys [NAP$^+$14], authorizing tests [BBD$^+$11, NAP$^+$14], etc.) assume that these parties do not collude with other entities.

Such an assumption has implications of various degrees in different contexts. For instance, [NAP$^+$14] assumes that a central authority is trusted to issue policies, (i.e., generating one-time decryption keys, allowing researchers to access a specific genome for a specific case). The CA is expected to be operated by some established entity such as the FDA, so that one can likely assume it has no incentive to misbehave (unless compromised). Similarly, protocols supporting large-cohort research, like the one in [XKB$^+$14], involve medical centers with little or no economic incentive to collude, break agreements, and proactively violate patients' privacy.

On the other hand, in some cases, non-collusion might be harder to enforce, while the consequences of collusion might be quite serious. For instance, the framework in [ARHR13] supports private disease susceptibility tests, and involves three entities: (i) the Patient, (ii) the MC, which administers the tests, and (iii) the SPU, which stores patients' encrypted SNPs. Data stored at the SPU is anonymized. However, if the SPU and MC collude, then the SPU can de-anonymize patients. Moreover, the MC's test specifics must be considered sensitive (e.g., a pharmaceutical company's intellectual property), otherwise there would be no point in performing *private* testing. This is because one could simply tell the patient/SPU which SNPs to analyze and run the test locally. However, patient and SPU collusion implies that confidentiality of the MC's test would be lost.

Also, solutions that assume third-party cloud storage providers do not collude with testing facilities, such as [KPK$^+$14], are limited to settings where one can truly exclude financial or law enforcement disincentives to collusion. If parties do collude, then the privacy of the patients could be violated.

Trusted Hardware. Other assumptions relate to secure hardware, like SGX, which isolates sensitive data into a protected enclave, thus supporting secure computation of the results, even if the machine is compromised. For instance, [CWJ$^+$17] relies on secure hardware to enable institutions to securely conduct computations over encrypted genomic data. We anticipate a greater volume of papers to be published over the next couple of years on the topic (in fact, particularly because the iDASH 2017 competition focused specifically on this issue [iDa17]). However, side-channel attacks have been recently demonstrated to be possible [BMD$^+$17, HCP17] and the full extent of SGX security has yet to be explored.

Threat Modeling. Finally, it is challenging in some settings to identify threat models. For instance, as mentioned earlier, the full extent of the inferences one can make from genomic data is still not clear. Consider for example GenoGuard [HAF$^+$15], which provides information-theoretic guarantees (and long-term security) in a threat model that needs to account for possible side-channel attacks. This is because, if the adversary knows some of the individ-

uals' physical traits (e.g., hair color or gender), then it can easily infer that the decryption key she is using is not the correct one. The authors attempt to address this issue by making their protocol phenotype-compatible for the cases of gender and ancestry, but there are many other traits in the human genome that possess probabilistic genotype-phenotype associations [LSM+17], thus making it extremely hard to address fully.

Take-Away 2. Work in genome privacy to date exhibits a clear trade-off between relying on non-trivial security assumptions and the practicality of the resulting solutions.

5.3   The Cost of Protecting Privacy

Genome privacy research mostly focuses on providing privacy-preserving versions of genomics-related functionalities, e.g., testing, data processing, and statistical research. While some of these functionalities are already in use (e.g., personal genomic tests offered by DTC companies, data sharing initiatives), others do not yet exist, at least in the way the genome privacy community has envisioned them. For instance, some investigations assume that individuals will soon be able to obtain a copy of their fully sequenced genome [BBD+11] or that we will be able to create an infrastructure and a market with dedicated providers to store and process genomic data for third-party applications [ARHR13, KPK+14].

Either way, recall that Table 1 attempts to evaluate the overhead incurred by privacy protection on efficiency and scalability, by comparing to that of supporting the corresponding functionality in a non privacy-preserving way. Similarly, we also attempt to quantify the loss in utility and flexibility.

Overheads. We find that, overall, high privacy overhead is linked to the use of expensive underlying cryptographic tools, e.g., ORAM, Pallier, and SWHE. On the one hand, one can be confident that some of these tools might become increasingly efficient given, thanks to breakthroughs on circuit optimization, e.g., secure computation techniques based on garbled circuits have become significantly faster [SHS+15] and oblivious transfer extensions [ALSZ13]. At the same time, the efficiency of fully homomorphic encryption has improved several orders of magnitude over the last couple of years [CGRS14, Tho16].

On the other hand, however, the characteristics of the privacy properties under consideration intrinsically make the problem harder. As a result, it is less likely that efficiency will eventually improve. For instance, in personal genomic testing, a basic privacy property is concealing which parts of the genome are being tested. This implies that every single part needs to be touched, even if the test only needs to examine a few positions. Some solutions [ARHR13, BBD+11] partially address this issue through means of pre-computation. Specifically, this is accomplished by encrypting genomic data so that it can be privately searched. However, the ciphertext still needs to be transferred in its entirety. Another example is in the context of genealogy testing, where the goal is to find

relatives and distant cousins [HFH+14]. Accomplishing this in the encrypted domain requires the presence of a central, non-colluding authority, which, as discussed above, is not always feasible. A similar situation arises in the context of data sharing: while secure two-party computation can efficiently support pairwise privacy-friendly information sharing, these do not scale well to a large number of participating entities.

Cloud Computing. We also observe that certain categories in Table 1 have more entries reporting high privacy overhead. This is inherent, for instance, for secure access and storage techniques, as, e.g., they result in a non-negligible expansion in storage complexity [ARH+14], rely on expensive tools like ORAM [KPK+14] to hide access patterns, or require expensive encoding [HAF+15]. Furthermore, secure outsourcing solutions use variants of fully homomorphic encryption (FHE) to support computation over encrypted data, which incur high computation complexity. In some cases, this casts doubt on their economic viability. More specifically, entities typically recur to cloud computing because it is cheaper and easier than having to set up high-performance computing infrastructures locally. However, cloud services usually charge customers per hour or per GB [Ama17]. Therefore, it may be counterintuitive, from an economic standpoint, for researchers to use these techniques if the overhead they introduce makes it cheaper to run computation locally.

Some of the privacy techniques we have analyzed in the context of secure outsourcing strive to reduce overhead by choosing FHE variants like SWHE [YSK+13, CKL15, KL15] and LHE [LLAN14], which are less expensive but less flexible in terms of computation they can support. Specifically, SWHE allows a limited number of operations to be evaluated, while LHE only supports limited circuit depth.

Data Representation. We also analyze the type of data each solution works with. For instance, some protocols operate on SNPs (e.g., [ARHR13, NAP+14]), while others support FSGs (e.g., [BBD+11, KPK+14]). On one hand, working with FSGs rather than only SNPs means that researchers and clinicians can consider the genome as a whole, supporting various services, such as research and testing relevant to rare genetic disorders. On the other hand, this might be challenging, especially in the ciphertext domain. For instance, genome sequencing is still not an error-free process: nucleotides (i.e., letters) are often misread by the sequencing machines, especially when operating at lower costs.[4] Additionally, deletions/insertions of nucleotides are not uncommon and the exact length of the human genome may vary among individuals. Handling with such issues is easier in-the-clear than in the ciphertext domain.

In some cases, solutions like [BBD+11] assume simplified formats where the genome is stored and processed as a long vector of nucleotides along with their exact position. Yet, when errors, deletions, or insertions are not identified before encryption, the accuracy of testing will dramatically reduce.[5]

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[4]Error reduction essentially relies on performing several reads in order to increase the confidence of the output.

[5]Testing in [BBD+11] requires access to specific positions of a vector con-

Also, important metadata contained in standard formats (such as, SAM, BAM, and FASTQ) is lost in such a custom representation. Moreover, a non-negligible portion of genome privacy investigations requires systems to change the way they store and process genomic data. This can also create challenging hurdles to adoption, especially considering that many are not compatible with each other.

Utility. Overall, Table 1 suggests that, in many instances, the loss in utility and flexibility, when comparing to the corresponding functionality in a non privacy-preserving setting, is high. For instance, this may arise due to data representation assumptions discussed above, or because the functionality needs to be adapted for privacy-enhancing tools to work. Consider the edit distance algorithm in [CKL15] can only support small parameters (thus, short sequences), while in [LLAN14] algorithms like Estimation Maximization need to be modified.

Finally, we remark that privacy protection inevitably yields a potential loss in utility, as the exact amount of information that can/should be disclosed needs to be determined ahead of time and rigorously enforced. This means that a clinician performing a test on the patient's genome loses the freedom to look at whichever data she might deem for diagnostic purposes. Similarly, a researcher looking for relevant data in large-cohorts might be limited in to what can be searched. A related consideration can be made with respect to data portability across different institutions, companies, or hospitals. For instance, if a patient's genomic information is encrypted and stored in a hospital's specialized unit (e.g., the SPU [ARHR13]), and the patient is traveling or visits another medical facility, it may be significantly harder to access and use her data.

Take-Away 3. Achieving adequate and effective privacy guarantees in the context of genomic testing is challenging due to the overhead incurred by the underlying privacy-enhancing technologies and the loss in utility and flexibility.

5.4 Challenges of Statistical Research

In Section 4, we reviewed certain efforts [JS13, USF13, THHA15] to achieve genome privacy using differentially private mechanisms. Though we did not include these in Table 1, they merit some consideration.

The Privacy vs Utility tension. The use of differential privacy in the context of statistical research is limited by the inherent trade-off between privacy and data utility. DP mechanisms aim to support the release of aggregate statistics while minimizing the risks of re-identification attacks. In this context, every single query yields some information leakage regarding the dataset, and, as the number of queries increases, so does the overall leakage. Therefore, to maintain the desired level of privacy, one has to add more noise with each query, which can degrade the utility of the mechanism. The privacy-vs-utility trade-off is a common theme in DP, and not

just in the context of genomics, although in many settings genomic data can be present unique characteristics with respect to its owner, thus further compounding the problem.

This challenge is exemplified in a case study by Fredrikson et al. [FLJ$^+$14], who focus on a DP release of models for personalized Warfarin dosage. In this setting, DP is invoked to guarantee that the model does not leak which patients' genetic markers were relied upon to build the model. In essence, they show that, to effectively preserve privacy, the resulting utility of the model would be so low that patients would be at risk of strokes, bleeding events, and even death. Overall, it is challenging to convince biomedical researchers, who are striving to achieve the best possible results, to accept a non-negligible toll on utility. This may justify why DP has not yet been used in practice in the context of genome research.

Specific use cases. In some settings, privacy and utility requirements might not be fundamentally at odds, and could be balanced with an appropriate privacy budget. For instance, [USF13] shows that adding noise directly to the χ^2-statistics, rather than on the raw values, yields better accuracy, while [JS13] demonstrates that the accuracy of the private statistics increases with the number of patients involved in the study. Also, Tramèr et al.'s techniques [THHA15] can achieve higher utility than [USF13, JS13] by *bounding* the background knowledge of the adversary. We believe this is reasonable in the short-term but less so in the long-term, as the adversary might obtain increased knowledge about the target (e.g., her SNPs).

Take-Away 4. Solutions based on noise for providing privacy in statistical research are inherently difficult to achieve due to the high dimensional characteristics of genomic data, which makes it challenging to stay ahead of the privacy-utility trade-off.

6 Discussion

Based on the results of our systematization effort, we provide several observations and recommendations about genome privacy research as a whole, focusing on its maturity and relevance.

Maturity. In Section 5, we discuss a number of non-trivial limitations faced by genome privacy work. One challenge stems from the lack of long-term security protection. This is non-trivial to address because available cryptographic tools are not suited for this goal. We also observe that the overwhelming majority of proposed techniques, striving for scalability, need to opt for weaker security guarantees (e.g., only considering semi-honest adversaries) or, worse yet, weaker models (e.g., assuming the presence of multiple non-colluding parties) to achieve workable solutions.

Overall, the underlying cryptographic tools affect efficiency and practicality, however, it is not always viable to envision ways to improve on them. While it is not unreasonable to expect breakthroughs from the cryptography community with respect to certain primitives (e.g., multi-party computation, homomorphic encryption, etc.), it is inherently difficult

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taining all nucleotides in the genome, thus, if an unidentified insertion or a deletion occurs, then the position would shift and the test would not work.

to address the limitations in terms of utility and/or flexibility on the actual functionality. When combined with assumptions made about the format and the representation of the data under analysis, this poses major hurdles against real-life adoption. Although a few efforts are promising, the readiness of PETs in the context of genomics is at a very conceptual level, with only a couple proof-of-concept exceptions.

Deployability. It is imperative to reason about the real-world relevance of PETs for genome privacy from a market standpoint. In this context, a good "measuring stick" may be work on genetic relatedness testing, where the potential drawbacks mentioned above (e.g., in terms of utility loss or computational overhead) might be less relevant than in clinical settings. Today, a growing market exists for ancestry and genealogy testing with companies like AncestryDNA and 23andMe, which provide cheap and seamless services, while investing substantial resources on improving user experience. Moreover, as their customer base grows, they can discover and match a greater number of relatives, as well as increase the accuracy of their models using metadata provided by the users. In return, these companies can profit from monetizing customers' data, e.g., by helping researchers recruit participants for research studies or providing pharmaceutical companies with access to data at a certain price [Pal15]. However, without access to data, their business model is not viable. This is specifically because deploying privacy-preserving relatedness testing would require the presence of entities that are willing to operate these services with no data monetization prospects. Notably, this is not a new issue in privacy, and similar considerations can be raised about research on privacy-preserving social networking or cloud computing, which has also struggled with adoption.

Pilot Studies. The monetary component might not necessarily apply in medical and clinical settings. For instance, many countries operate not for profit health service models, and put forward legislation strongly regulating privacy in healthcare. In this context, pilots might provide encouraging results. One such study is presented in a paper by McLaren et al. [MRA+16], which reports on a trial conducted at the CHUV hospital in Lausanne, Switzerland. Researchers have piloted the use of PETs to encrypt genetic markers of HIV-positive patients, allowing their doctors to obtain the results of various tests in a privacy-preserving way.[6] The study, however, also highlights a few challenges, including low acceptability from the physicians' point of view (nearly half reported that the test results were not useful and that they considered changing course of treatment in only 10% of the cases). Moreover, from a technical standpoint, the actual solution adopted does not provide long-term security and relies on non-collusion assumptions.

Relevance to current initiatives. We also question whether solutions introduced through genome privacy research could actually be used in practice, to enhance privacy in the context

of the main initiatives currently taking place to support collaborative genomics research. At the moment, these mainly deal with privacy by relying on access control mechanisms and informed consent, but ultimately require participants to voluntarily agree to make their genomic information available to any researchers who wish to study it.

Interestingly, in this context, we only came across one solution that could be leveraged for this purpose, although it would require infrastructure changes. Specifically, the controlled-functional encryption (C-FE) protocol presented in [NAP+14] would allow participants' data to be encrypted under a public key issued by a central authority. This would allow researchers to run tests using a one-time function key, obtained by the authority, which corresponds to a specific test and can only be used for that purpose. This means that the authority would need to issue a different key for each individual, for every request, and for every function. Unfortunately, this is not practical in the context of large-scale research involving millions of participants and hundreds (if not thousands) of researchers.

Addressing known attacks. On the other hand, some efforts have aimed to address specific attacks against data sharing initiatives, e.g., the membership inference attack to the Beacon network [SB15] (cf. Section 1). Recall that this system allows a researcher to query institutions about if they have information about certain mutations. Shringarpure and Bustamante's attack [SB15] shows that one can infer whether an individual is in a Beacon by repeatedly submitting queries for variants which are present in the genome of the individual. Aiming to address this attack, Raisaro et al. [RTJ+17] propose that a Beacon should answer positively only if the individuals containing the queried mutation are more than one. They also propose hiding a portion of unique alleles using a binomial distribution and providing false answers to queries targeting them, or imposing a "query budget." Additionally, Wan et al. [WVKM17] measure the discriminative power of each single nucleotide variant (SVN) in identifying an individual in a Beacon, and set to flip the top SNVs according to a differential discriminative power, measuring the effects in privacy and utility. However, both solutions, similar to the limitations discussed in Section 5.3, make important trade-offs with respect to utility to limit the extent of the attacks. More specifically, [RTJ+17] alters or limits the responses of the network, while [WVKM17], acknowledging that utility loss is unavoidable, provides ways to calculate (but not solve) this trade-off.

7 Conclusion

This paper introduced and applied a structured methodology to systematize knowledge around genome data privacy research. We focused on investigations using technologies to enhance privacy in the genomic context and performed a deep dive on specific selected results that serve as a representative sample of the community's work. We defined systematic criteria and compiled a concise table (Table 1), which provides

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[6]Tests include virus progression and response to therapy, pharmacokinetics assessment of a few drugs, and presence of metabolic traits.

insight on the maturity and the relevance of the privacy enhancing solutions produced thus far, as well as their inherent challenges and trends. As our taxonomy is not chronologically bounded, it can be reused, in a few years, by other researchers aiming to revisit new results and assess the progress in the field.

Our analysis indicated that PETs proposed in the context of genome privacy only offer protection in the short-term, as they are not designed to last longer than a couple of decades. We also expanded on assumptions made by the community, as well as the costs introduced by privacy defenses in terms of overheads and loss in utility and flexibility.

Although our systematization highlights a number of challenges and limitations of the genome privacy body of work, we are also confident that a significant portion of research can be used to enable genomics-related applications that are not possible at the moment because of legal and policy restrictions. For instance, genetic and health data cannot easily cross borders, which makes international collaborations very challenging. In this context, mechanisms provably guaranteeing privacy-friendly processing of genomic data may alleviate these restrictions and enable important research progress, and we hope to see more pilot studies along these lines in the near future.

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