Attacks on genetic privacy via uploads to genealogical databases

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Abstract

Direct-to-consumer (DTC) genetics services are increasingly popular for genetic genealogy, with tens of millions of customers as of 2019. Several DTC genealogy services allow users to upload their own genetic datasets in order to search for genetic relatives. A user and a target person in the database are identified as genetic relatives if the user's uploaded genome shares one or more sufficiently long segments in common with that of the target person—that is, if the two genomes share one or more long regions identical by state (IBS). IBS matches reveal some information about the genotypes of the target person, particularly if the chromosomal locations of IBS matches are shared with the uploader. Here, we describe several methods by which an adversary who wants to learn the genotypes of people in the database can do so by uploading multiple datasets. Depending on the methods used for IBS matching and the information about IBS segments returned to the user, substantial information about users' genotypes can be revealed with a few hundred uploaded datasets. For example, using a method we call IBS tiling, we estimate that an adversary who uploads approximately 900 publicly available genomes could recover at least one allele at SNP sites across up to 82% of the genome of a median person of European ancestries. In databases that detect IBS segments using unphased genotypes, approximately 100 uploads of falsified datasets can reveal enough genetic information to allow accurate genome-wide imputation of every person in the database. We provide simple-to-implement suggestions that will prevent the exploits we describe and discuss our results in light of recent trends in genetic privacy, including the recent use of uploads to DTC genetic genealogy services by law enforcement.

1 Introduction

As genotyping costs have fallen over the last decade, direct-to-consumer (DTC) genetic testing (Hogarth et al., 2008; Hogarth and Saukko, 2017; Khan and Mittelman, 2018) has become a major industry, with over 26 million people enrolled in the databases of the five largest companies

(Regalado, 2019). One of the major applications of DTC genetics has been genetic genealogy. Customers of companies such as 23andMe and Ancestry, once they are genotyped, can view a list of other customers who are likely to be genetic relatives. These putative relatives' full names are often given, and sometimes contact details are given as well. Such genealogical matching services are of interest to people who want to find distant genetic relatives to extend their family tree, and can be particularly useful to people who otherwise may not have information about their genetic relatives, such as adoptees or the biological children of sperm donors. Several genetic genealogy services—including GEDmatch, MyHeritage, FamilyTreeDNA, and LivingDNA (Table 1)—allow users to upload their own genetic data if they have been genotyped by another company. These entities generally offer some subset of their services at no charge to uploaders, which helps to grow their databases. Upload services have also been used by law enforcement, with the goal of identifying relatives of the source of a crime-scene sample (Erlich et al., 2018; Edge and Coop, 2019), prompting discussion about genetic privacy (Court, 2018; Ram et al., 2018; Kennett, 2019; Scudder et al., 2019).

The genetic signal used to identify likely genealogical relatives is identity by descent (IBD, Browning and Browning 2012; Thompson 2013. We use "IBD" to indicate both "identity by descent" and "identical by descent," depending on context.) Pairs of people who share an ancestor in the recent past can share segments of genetic material from that ancestor. The distribution of IBD sharing as a function of genealogical relatedness is well studied (Donnelly, 1983; Huff et al., 2011; Browning and Browning, 2012; Thompson, 2013; Buffalo et al., 2016; Conomos et al., 2016; Ramstetter et al., 2018), and DTC genetics entities can use information about the number and length of inferred IBD segments between a pair of people to estimate their likely genealogical relationship (Staples et al., 2016; Ramstetter et al., 2017). These shared segments—IBD segments—result in the sharing of a near-identical stretch of chromosome (a shared haplotype). Shared haplotypes can most easily be identified looking for long genomic regions where two people share at least one allele at nearly every locus.

For the rest of the main text, we focus on identical-by-state (IBS) segments, which are genomic runs of (near) identical sequence shared among individuals and can be thought of as a superset of true IBD segments. Very long IBS segments, say over 7 centiMorgans (cM), are likely to be IBD, but shorter IBS segments, say <4 cM, may or may not represent true IBD due to recent sharing—they may instead represent a mosaic of shared ancestry deeper in the past. Many of the algorithms for IBD detection that scale well to large datasets rely principally on detection of long IBS segments, at least as their first step (Gusev et al., 2009; Henn et al., 2012; Huang et al., 2014). We consider the effect on our results of attempting to distinguish IBS and IBD in the supplementary material.

Many DTC genetics companies, in addition to sharing a list of putative genealogical relatives, give customers information about their shared IBS with each putative relative, possibly including the number, lengths, and locations of shared genetic segments (Table 1). This IBS information may represent substantial information about one's putative relatives—one already has access to one's own genotype, and so knowing the locations of IBS sharing with putative relatives reveals information about those relatives' genotypes in those locations (He et al., 2014). Users of genetic genealogy services implicitly or explicitly agree to this kind of genetic information sharing, in which large amounts of genetic information are shared with close biological relatives and small amounts of information are shared with distant relatives.

Here we consider methods by which it may be possible to compromise the genetic privacy of

Service	Database Size (millions)	Individuals Shown	IBS/IBD Segments Reported
GEDmatch	1.2	3,000 closest matches shown free; Unlimited w/ $10/month license; any two kits can be searched against each other	Yes if longer than user-set threshold. Min. threshold 1cM, default 7cM
FamilyTreeDNA	1*	All that share at least one 9cM block or one 7.69cM block and 20 total cM	Yes, down to 1cM, for $19 per kit
MyHeritage	3	All that share at least one 8cM block	Yes, down to 6cM, for $29 per kit or unlimited for $129/year. Customers may opt out
LivingDNA	Unknown	Putative relatives out to ≈ 4th cousin	Only sum length of matching segments reported
DNA.LAND**	0.159	Top 50 matches shown with minimum 3cM segment	Yes

Table 1: Key parameters for several genetic genealogy services that allow user uploads as of July 26th, 2019. *Though Regalado (2019) reports that FamilyTreeDNA has two million users, he also suggests that only about half of these are genotyped at genome-wide autosomal SNPs, which is in line with other estimates (Larkin, 2018). **DNA.LAND has discontinued genealogical matching for uploaded samples as of July 26th, 2019.

users of genetic genealogy databases. In particular, we show that for services where genotype data can be directly uploaded by users, many users may be at risk of sharing a substantial proportion of their genome-wide genotypes with any party that is able to upload and combine information about several genotypes. We consider two major tools that might be used by an adversary to reveal genotypes in a genetic genealogy database. One tool available to the adversary is to upload real genotype data or segments of real genotype data. When uploading real genotypes, the information gained comes by virtue of observed sharing between the uploaded genotypes and genotypes in the database (an issue also raised by Larkin, 2017). Publicly available genotypes from the 1000Genomes Project (1000 Genomes Project Consortium, 2012), Human Genome Diversity Project (Cann et al., 2002), OpenSNP project (Greshake et al., 2014), or similar initiatives might be uploaded.

A second tool available to the adversary is to upload artificial genetic datasets (Ney et al., 2018). In particular, we consider the use of artificial genetic datasets that are tailored to trick algorithms that use a simple, scalable method for IBS detection, that of identifying long segments in which a pair of genomes contains no incompatible homozygous sites (Henn et al., 2012; Huang et al., 2014). Such artificial datasets can be designed to reveal the genotypes of users at single sites of interest or sufficiently widely spaced sites genome-wide. We describe how a set of a few hundred artificial datasets could be designed to reveal enough genotype information to allow accurate imputation of common genotypes for every user in the database.

Below, we describe these procedures and illustrate one of them in publicly available data. We have not attempted any of these methods in any DTC database, and we contacted representatives of each of the entities listed in Table 1 90 days before posting this manuscript (July 24th, 2019) in order to provide them time to shore up any vulnerabilities related to the exploits we describe. We show that under some circumstances that fall within the current or past practices of various DTC genetics upload services, many users could be at risk of having their genotypes revealed, either at key positions or at many sites genome-wide. In the discussion, we consider this work in light of other genetic privacy concerns (Erlich and Narayanan, 2014; Naveed et al., 2015), and we give some suggested practices that DTC genetics services can adopt to prevent privacy breaches by the techniques described here.

2 Results

We describe three general methods for revealing the genotypes of users in genetic genealogy databases that allow uploads. The first, **IBS tiling**, involves uploading many real genotypes in order to identify genotype information from many regions in many people. The second, **IBS probing**, involves uploading a haplotype containing an allele of interest along with other genotypes that are unlikely to be IBS with any user in the database. Matches with the uploaded dataset are thus likely to be users who carry the allele of interest. The third method, **IBS baiting**, involves uploading fake datasets with long runs of heterozygosity to induce phase-unaware methods for IBS calling to reveal genotypes.

2.1 IBS tiling

In IBS tiling, the genotype information shared between a target user in the database and each member of a set of comparison genomes is aggregated into potentially substantial information about the target's genotypes. For example, consider a user of European ancestries. She is likely to have some degree of IBS sharing with a large set of people from across Europe (Ralph and Coop, 2013) (and beyond). If one knows the user's IBS sharing locations with one random person of European ancestries (and the random person's genotype), then one can learn a little about the user's genotype. But if one can upload many people's genotypes for comparison, then one can uncover small proportions of the target user's genotypes from many of the comparison genotypes, eventually uncovering much of the target user's genome by virtue of a "tiling" of shared IBS with known genotypes (Figure 1A). A similar idea has been suggested with application to IBD-based genotype imputation (Carmi et al., 2014).

We consider the amount of IBS tiling possible within a set of publicly available genotypes for 872 people of European origin genotyped at 544,139 sites. We phased the sample using Beagle 5.0 (Browning and Browning, 2007) and used Refined IBD software (Browning and Browning, 2013) to identify IBS segments (see Methods). In the main text, we include IBS segments that are not particularly likely to be IBD—these are IBS segments returned by Refined IBD with relatively low LOD scores for IBD, between 1 and 3. We consider the results obtained after filtering segments likely to be true IBD in Figure S1 of the supplement.

Once we identified IBS segments shared among the 872 people in our sample, we asked about the amount of genotype information that could be identified using IBS tiling. The amount of genotype information obtainable is strongly influenced by two factors: the size of the comparison set used (i.e., the number of people used to identify IBS segments with a target sample), and the

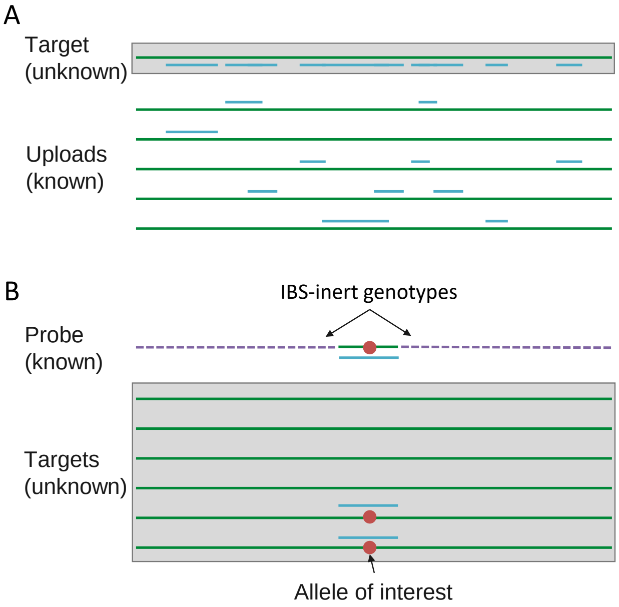

Figure 1: Schematics of the IBS tiling and IBS probing procedures. (A) In IBS tiling, multiple genotypes are uploaded (green lines) and the positions at which they are IBS with the target (represented by blue lines) are recorded. Once enough datasets have been uploaded, the target will eventually have a considerable proportion of their genome "tiled" by IBS with uploads that have known genotypes. (B) In IBS probing, the uploaded probe consists of a haplotype carrying an allele of interest (red dot) surrounded by "IBS-inert" segments (purple dashed lines)—fake genotype data designed to be unlikely to share any IBS regions with anyone in the database. In the event of an IBS match in the database, the matching database entry is likely to carry the allele of interest.

restrictiveness of the criteria by which IBS segments are identified. For example, if only long IBS segments are shown to users, then the proportion of a typical person's genotype data obtainable will be smaller than if short IBS segments are also shown. The minimum IBS length reported by several genetic genealogy services as of July 26th, 2019 is shown in Table 1.

Figure 2 shows the median amount of coverage obtainable by IBS tiling as a function of comparison sample size, imposing various restrictions on the minimum segment length in cM. (For similar results, see Figure 2b of Carmi et al. (2014) and Figure 2 of Panoutsopoulou et al. (2014).) Approximately 2.8 Giga base-pairs (Gbp) were covered by IBS segments anywhere in the genome among any pair of chromosomes from distinct people; we take this to be approximately the maximum possible genomic length recoverable by IBS with our SNP set. Using the entire sample (giving a comparison sample of 871, since the target is left out) and including all called IBS segments $>$1 cM, the median person has an average of 60% of the maximum length of 2.8 Gbp covered by IBS segments (with the average taken across their two chromosomes), and sites across 82% of this length will have at least one of two alleles recoverable by IBS tiling. Increasing the cM threshold required for reporting substantially reduces the amount of IBS tiling. With a cutoff of 3 cM, approximately 6.9% of the median person's genotype information is recoverable, including at least one of two alleles at sites in 11% of the genome. When a more stringent cutoff

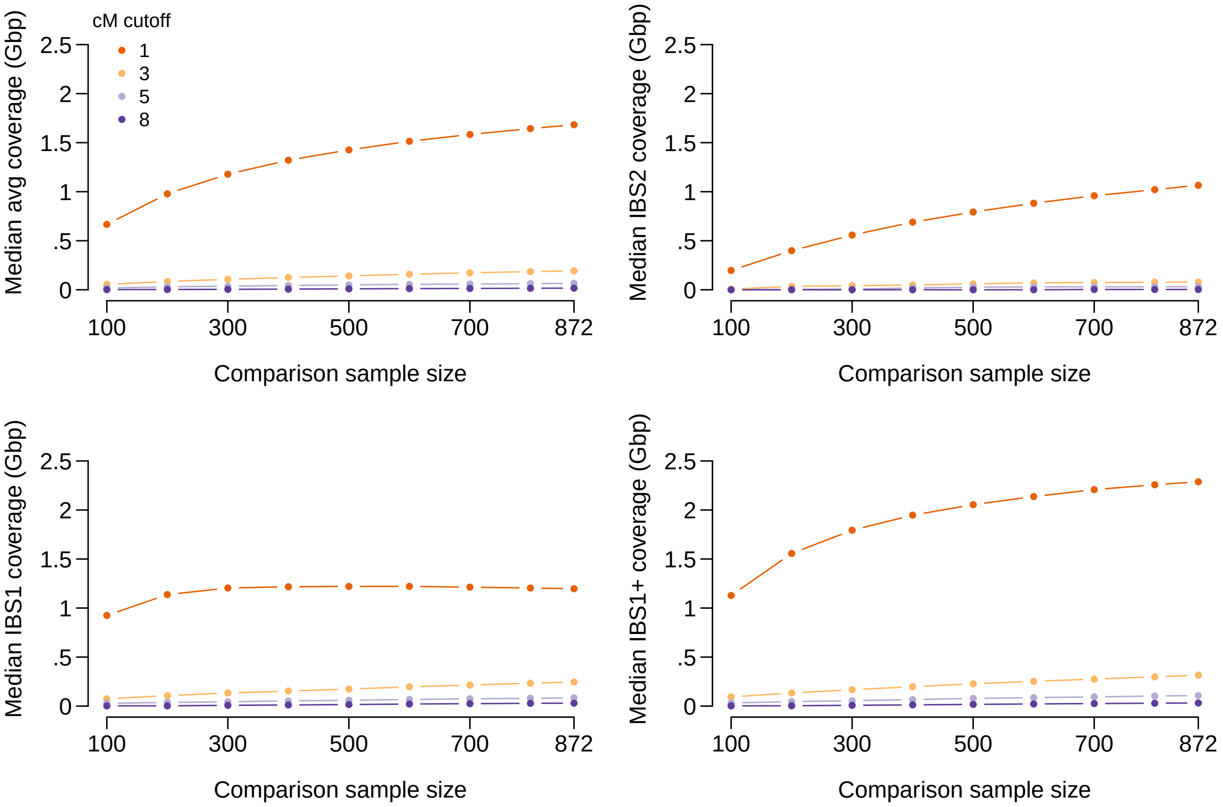

Figure 2: Lengths of genome in Giga base-pairs (Gbp) covered by IBS tiling as a function of minimum required length of IBS segments in centiMorgans (cM) and size of a randomly selected comparison sample for the median person in our dataset. The top-left panel shows the average coverage across each of the person's two haplotypes. The top-right shows IBS2 coverage, the length of genome where both haplotypes are covered by IBS tiles. The bottom-left panel shows IBS1, the length of genome where exactly one haplotype is covered by IBS tiles. (IBS1 coverage can decrease at larger comparison sample sizes because IBS2 coverage increases.) The bottom-right panel shows IBS1+ coverage, the length of genome covered by either IBS1 or IBS2.

of 8 cM is used, only 1% of the genome has at least one of two alleles recoverable for the median person when using a comparison sample of 871. Our reports for segments longer than 3 cM may be conservative because Refined IBD sometimes splits long IBS segments into multiple shorter segments in the presence of phasing errors (Browning and Browning, 2013; Bjelland et al., 2017).

For some people, the amount of information obtainable by IBS tiling will be even larger. In our sample, the top 10% of people have genotypes across 76% of their total genome covered by IBS tiles, including one or more alleles at sites in at least 93% of the 2.8 Gbp covered by IBS tiles anywhere. If only segments longer than 3 cM are reported, the top 10% of people have one or both alleles covered at sites in at least 38% of the total, and if only segments longer than 8 cM are reported, the top 10% have one or both alleles covered at sites in at least 6% of the total.

The coverage obtained by IBS tiling and its informativeness about target genotypes depends on the specific practices used for reporting IBS information (Figures S1-S4). For example, some DTC genealogy services only report matching segments for pairs of people who share at least one long IBS segment (Table 1), but then allow users to see shorter IBS segments (> 1cM) for those pairs of people. Unsurprisingly, we find that this strategy allows a much higher level of IBS tiling than if only long segments are revealed (Figure S2), because people who share a long IBS segment may also share shorter segments that are hidden if only long segments are reported.

In this demonstration of IBS tiling, we used haplotype information provided by the Refined IBD software to determine which haplotypes were covered by IBS in each person. Some genetic genealogy services that provide information on the location of IBS matches with putative relatives do not provide haplotype information, making it difficult to distinguish IBS1 (in which one chromosome is covered by an IBS segment) and IBS2 (in which both chromosomes are covered by IBS segments). One tool available to an adversary pursuing IBS tiling is to upload genotype information that is homozygous at all sites using one of two phased haplotypes as a basis, effectively searching for IBS with one chromosome at a time. In the presence of phasing errors, some IBS segments may be missed, but the decrease in tiling performance is small for short segments (Figure S3). It may remain difficult to distinguish some cases—such as distinguishing IBS1 from IBS2 with a run of homozygosity on the database genotype—but there will be no question about which uploaded haplotype is IBS with the database genotype. Thus, at any point where a homozygous upload and a target are IBS, at least one of the target's alleles is known. Further, if the target is IBS with any other uploaded datasets at a genetic locus of interest, it will often be possible to infer the target's full genotype.

2.2 IBS probing

IBS probing is an application of the same idea underlying IBS tiling. By IBS probing, one could identify people with specific genotypes of interest, such as risk alleles for Alzheimer's disease (Corder et al., 1993). To identify people carrying a particular allele at a locus of interest, one could use haplotypes carrying the allele in publicly available databases. To do so, one would extract a haplotype that surrounds the allele of interest and place it into a false genetic dataset designed to have no long IBS segments with any real genomes (Figure 1B). Thus, any returned putative relatives must match at the allele of interest, revealing that they carry the allele. We call this attack "IBS probing" by analogy with hybridization probes, as the genuine haplotype around the allele of interest acts as a probe. Whereas IBS tiling recovers genetic information from across the genome, IBS probing acts only on a single locus of interest. The advantage is that IBS probing is possible even in databases that do not report the chromosomal locations of IBS segments.

There are several ways of generating chromosomes unlikely to have long shared segments with any entries in the database. One simple way is to sample alleles at each locus in proportion to their frequencies. Chromosomes generated in this way are free of linkage disequilibrium (LD) and thus unlike genuine chromosomes. If the database distinguishes between IBS and IBD, then these fake data are unlikely to register as IBD with any genuine haplotypes. However, they may appear as IBS in segments where genetic diversity is low, depending on the length threshold used by the database. Near-zero rates of IBS can be obtained by generating more unusual-looking fake data, such as by sampling alleles from one minus their frequency or by generating a dataset of all minor alleles.

Figure 3 shows a demonstration of IBS probing performance in our set of 872 Europeans in a window around the APOE locus. For a 1cM threshold for reporting IBS, we generated probes

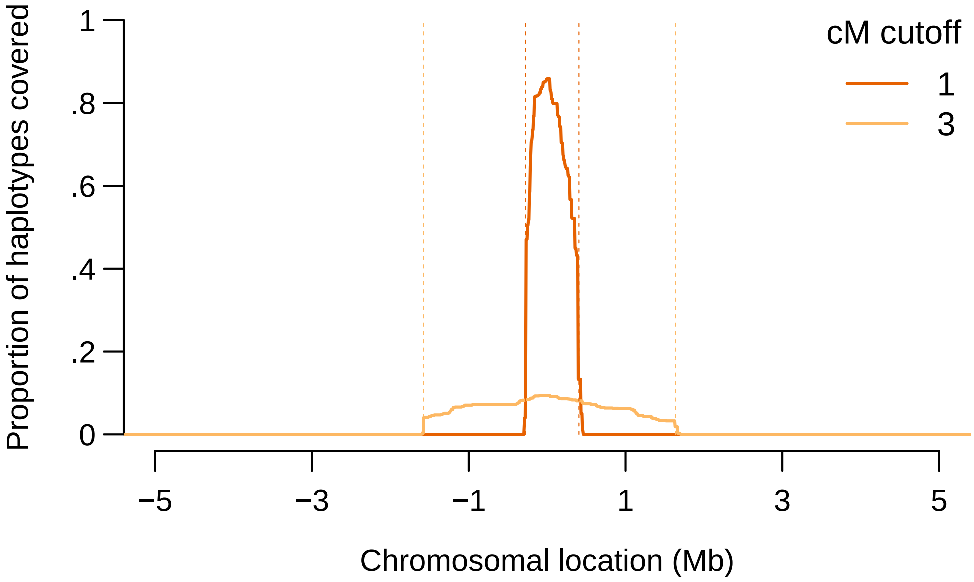

Figure 3: A demonstration of the IBS probing method around position 45411941 on chromosome 19 (GRCh37 coordinates), in the APOE locus. We show the proportion of haplotypes among the 872 Europeans in our sample covered IBS by probes constructed from the sample, as a function of the chromosomal location in a 10-Mb region around the site of interest. In orange, we show the coverage using a 1cM threshold for reporting IBS, where the probes are constructed using real data in a 1.9-cM region centered on the site of interest (region boundaries shown in dashed orange). In yellow, we show the coverage using a 3cM threshold for reporting IBS, where the probes are constructed using real data in a 5.9-cM region around the site of interest.

by retaining 1.9cM of real data around a site of interest in the APOE locus from all 872 people. Outside that 1.9cM window, we generated data by drawing alleles randomly (see Methods). For a 3cM threshold for reporting IBS, we generated probes by retaining 5.9cM of real data around the site of interest. With 1cM matching, 1497 of 1744 haplotypes (86%) matched one of the probes at the site of interest. (Target haplotypes were not allowed to match probes constructed from the same person that carried the target haplotype.) With 3cM matching, 164 of 1744 haplotypes (9.4%) matched one of the probes at the site of interest. Very few matches occurred outside the region of interest—none with a 3cM threshold and only 0.1% of matches with a 1cM threshold. Moreover, we generated different inert genotypes for all 872 probes, and the great majority of these had no matches with any real dataset. An adversary would only need to generate one inert dataset, which can be tested by uploading to the database and confirming that no matches are returned. Probes could then be constructed by stitching real haplotypes at the site of interest into the the same set of inert data. The probes would then be likely to match each other, but the adversary would know those identities and could ignore those matches.

The efficacy of IBS probing will depend on the minimum IBS-match length reported to users, the specific methods used for identifying IBS segments (Figures S6-S5), and whether the genotype of interest is included on the SNP chip. For example, high thresholds for IBS reporting will mean that uploaded genotypes will need to have long IBS segments with targets at the locus of interest. Long IBS segments are likely to represent relatively close genealogical relatives (i.e., long IBS segments are likely to be IBD segments), and not many targets will be close relatives of the source of any given haplotype of interest. If the locus of interest is not included on the chip used to genotype either the uploaded sample or the target sample, then probing may only expected to work well if the upload and the target are IBD rather than merely IBS. Limiting probing results to likely IBD matches will decrease the number of matches returned, particularly for short cM thresholds (Figure S5).

Another factor that will affect the success of IBS probing is the frequency of the allele of interest. For example, if the allele of interest is very rare, then it is likely to be only somewhat enriched on the haplotypes that tend to carry it, and reported matches may not actually carry the allele, even if they are IBD with an uploaded haplotype that carries it. IBS probing will perhaps be most efficient when the allele of interest is both common and relatively young, as is the case for founder mutations. In this case, most carriers of the allele will share the same long haplotype around the site of interest, meaning that fewer probes would need to be uploaded in order to learn the identities of the majority of the carriers in the database.

2.3 IBS baiting

IBS tiling and IBS probing take advantage of publicly available genotype data. The idea of both is that an adversary uploads genuine genetic datasets—or, in the case of IBS probing, datasets with genuine segments—to learn about entries in the database that share segments with the uploaded genomes.

In this section, we describe an exploit called IBS baiting. The specific strategy for IBS baiting that we describe may be possible if the database identifies putative IBS segments by searching for long regions where a pair of people has no incompatible homozygous sites. An incompatible homozygous site is a site at which one person in the pair is homozygous for one allele, and the other person is homozygous for the other allele. Identifying IBS segments in this way does not require phased genotypes and scales easily to large datasets—we refer to methods in this class as "phase-unaware" and contrast them with phase-aware methods for IBS detection. Phase-unaware methods are robust to phasing errors, which are an issue for long IBD segments (Durand et al., 2014). Major DTC genetics companies have used phase-unaware methods in the past for IBS detection (Henn et al., 2012; Hon et al., 2013), and some state-of-the-art IBD detection and phasing pipelines feature an initial phase-unaware step (Huang et al., 2014; Loh et al., 2016).

The main tool used in IBS baiting is the construction of apparently IBS segments by assigning every uploaded site in the region to be heterozygous. These runs of heterozygosity, which are unlikely to occur naturally (unlike runs of homozygosity, McQuillan et al., 2008; Pemberton et al., 2012), will be identified as IBS with every genome in the database using phase-unaware methods: because they contain no homozygous sites at all, they cannot contain incompatible homozygous sites with any person in the database.

Here, we consider a database using the simplest possible version of a phase-unaware method for detecting IBS, in which an apparent IBS segment is halted exactly at the places at which the first incompatible homozygous site occurs on each side of the segment. (We also assume that the database detects all segments without incompatible homozygous sites that pass the required length threshold.) In principle, such IBS-detection algorithms can be altered to allow for occasional incompatible homozygous sites before halting as an allowance for genotyping error, or the extent of the reported region might be modified to be less than the full range between

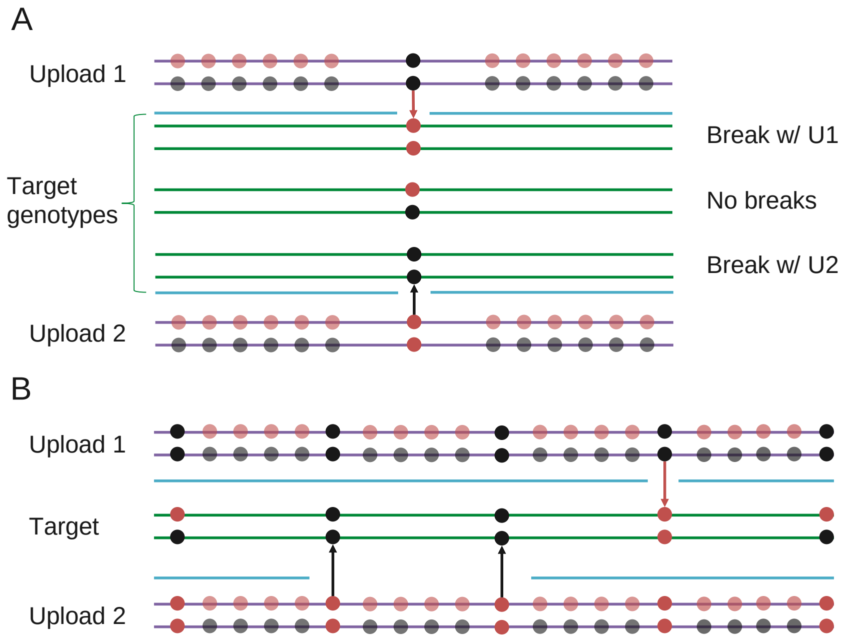

Figure 4: Schematics of the IBS baiting procedure. (A) To perform IBS baiting at a single site, two uploads are required, each with runs of heterozygous genotypes flanking the key site. At the key site, the two uploaded datasets are homozygous for different alleles. The three possible target genotypes at the key site can each be determined by examining their IBS coverage with the uploads. If there is a break in IBS with either upload, then the target is homozygous for the allele not carried by the upload that shows the break in IBS (with the broken IBS segment shown as a cyan line). If there is no break in IBS with either upload, then the target is heterozygous at the key site. (B) Target genotypes at many key sites across the genome can be learned by comparison with two uploaded datasets, as long as key sites are spaced widely enough.

incompatible homozygous sites. Versions of IBS baiting might be developed to work within such modifications.

2.3.1 Single-site IBS Baiting

The simplest application of IBS baiting is to use it to reveal genotypes at a single site. If IBS is identified by looking for single incompatible homozygous sites, then users' genotypes at any single biallelic site of interest can be determined by examining their putative IBS with each of two artificial datasets (Figure 4A). In each artificial dataset, the site of interest is flanked by a run of heterozygosity. The combined length of these two runs of heterozygosity must exceed the minimum length of IBS segment reported by the database. The adversary uploads two datasets with these runs of heterozygosity in place. In one dataset, the site of interest is homozygous for the major allele, and in the other, the site of interest is homozygous for the minor allele. If the target user is homozygous at the site of interest, then one of these two uploads will not show a single, uninterrupted IBS segment—it will be interrupted at the site of interest. If the IBS segment with the dataset homozygous for the major allele is interrupted, then the target user is homozygous for the minor allele. Similarly, if the IBS segment with the dataset homozygous for the minor allele is interrupted, then the target user is homozygous for the major allele. If neither IBS segment is interrupted, then the target user is heterozygous at the site of interest. Thus, for any genotyped biallelic site of interest, the genotypes of every user shown as a match can be revealed after uploading two artificial datasets. Depending on how possible matches are made accessible to the adversary, the genotypes of every user could be returned. Genotypes of medical interest that are often included in SNP chips, such as those in the APOE locus (Corder et al., 1993), are potentially vulnerable to single-site IBS baiting.

Single-site IBS baiting could also be used if chromosomal locations of matches are not reported. To do so, one would use the the scheme we describe in a large region surrounding the locus of interest and use fake IBS-inert segments to fill in the rest of the dataset.

2.3.2 Parallel IBS Baiting

The second method we consider applies the IBS baiting technique to many sites in parallel (Figure 4B). By parallel application of IBS baiting, users' genotypes at hundreds or thousands of sites across the genome can be identified by comparison with each pair of artificial genotypes. By repeated parallel IBS baiting, eventually enough genotypes can be learned that genotype imputation becomes accurate, and genome-wide genotypes could in principle be imputed for every user in the database. If IBS segments as short as 1cM are reported to the user, then accurate imputation (97-98% accuracy) becomes possible after comparison with only ≈100 uploaded datasets. The procedure starts by designing a single pair of uploaded files as follows:

1. Identify a set of key sites to be revealed by the IBS baiting procedure. For every key site, the sum of the distances in cM to the nearest neighboring key site on each side (or the end of the chromosome, if there is no flanking key site on one side) must be at least the minimum IBS length reported by the database.

2. Produce two artificial genetic datasets. In each, every non-key site is heterozygous. In one, each key site is homozygous for the major allele, in the other, each key site is homozygous for the minor allele.

3. Upload each artificial dataset and compare them to a target user. Key sites that are covered by putative IBS segments between the target and both artificial datasets are heterozygous in the target. The target is homozygous for the major allele at key sites that are covered by putative IBS segments between the target and the major-allele-homozygous dataset only. Similarly, the target is homozygous for the minor allele at key sites that are covered by putative IBS segments between the target and the minor-allele-homozygous dataset only.

Carrying out this procedure reveals the target's genotype at every key site. If IBS segments of length at least t cM are reported, and a chromosome is c cM long, then up to $2c/t-1$ key sites can be revealed with each pair of uploaded files. (To see this, consider the case where $c = tk$, with k a positive integer, and place key sites at $t/2, t, 3t/2, ..., c-t/2$.) This means that with a minimum reported IBS threshold of 1cM, 100 uploaded datasets could reveal approximately 100 genotypes per cM, which is enough to impute genome-wide genotypes at $97-98\%$ accuracy (Shi et al., 2018). In principle, the key sites could also be chosen to ensure good LD coverage and higher imputation accuracy. Of course, higher accuracy imputation can be obtained by recovering exact genotypes for more sites, and with several thousand uploads, the genotypes at every genotyped site could be revealed by IBS baiting without the need to impute.

3 Discussion

We have suggested several methods by which an adversary might learn the genotypes of people included in a genetic genealogy database that allows uploads. Our methods take advantage of both the population-genetic distributions of IBS segments and of methods used for calling IBS. In particular, IBS tiling works simply because there are background levels of IBS (and IBD) even among distantly related members of a population (e.g. Ralph and Coop, 2013). In our dataset, the median person had the majority of their genetic information susceptible to IBS tiling on the basis of other members of the dataset, depending on the procedures used for reporting IBS. (We consider some alternative IBS reporting procedures in the supplement.) IBS tiling performance will also depend on the ancestries of the target and comparison samples because IBD rates differ within and among populations (Palamara et al., 2012; Carmi et al., 2013; Ralph and Coop, 2013), as well as on the prevalence of genealogical relatives in the dataset. (We used publicly available datasets from which close relatives had already been pruned.) IBS tiling performance improves as the size of the comparison sample increases. Thus, if enough genomes are compared with a target for IBS, eventually a substantial amount of the target genome is covered by IBS with one or more of the comparison genomes.

IBS probing combines the principles behind IBS tiling with the idea of "IBS-inert" artificial segments. If the majority of the genome—everywhere except a locus of interest—can be replaced with artificial segments that will not have IBS with any genome in the database, then the adversary knows that any matches identified are in a locus of interest. As such, IBS probing could be used to reveal sensitive genetic information about database participants even if chromosomal locations of matches are not reported to users.

Finally, IBS baiting exploits phase-unaware IBS calling algorithms that use incompatible homozygous sites to delimit putative IBS regions. Whereas such methods are useful in genetic genealogy because they scale well to large data, they are vulnerable to fake datasets that include runs of heterozygous sites, which will be identified as IBS with everyone in the database. By inserting homozygous genotypes at key sites and heterozygotes everywhere else, we estimate that approximately 100 well-designed uploads could reveal enough genotypes to impute genome-wide information for any user in a database, provided that the threshold for reporting a matching segment is ≈ 1 cM. Similarly, two uploads could reveal any genotype at a single site of interest, such as rs429358, which reveals whether the user carries an APOE-ϵ4 variant and is associated with risk of late-onset Alzheimer's disease.

There are millions of people enrolled in genetic genealogy databases that allow uploads (Table 1). Genetic genealogy has many applications, and uploads are popular with users who want to find relatives who may be scattered across different databases. Though allowing uploads brings several benefits for both customers and DTC companies, it also entails additional privacy risks. Users of DTC genetic genealogy services that allow uploads could be at risk of having their genetic information extracted by the procedures we describe here, depending on the methods that these services use to identify and report IBS. Concerns arising from the methods we report are in addition to standard digital security concerns. The attacks we describe require little special expertise in computing; the adversary only needs to be able to procure or create the appropriate data files and to process and aggregate the information returned from the database.

We have not set out to determine precisely how vulnerable users of each specific DTC service are. We do not know the full details of methods used by each service for matching, nor have we attempted to deanonymize any real users' genotypes. We contacted representatives of each of the organizations listed in Table 1 90 days (July 24th, 2019) before posting this manuscript publicly in order to give them time to repair any security vulnerabilities related to the methods we describe here. DTC genetic genealogy is a growing field, and any new entities that begin offering upload services may also face threats of the kind we describe.

Genetic genealogy databases that allow uploads have been in the public eye recently because of their role in long-range familial search strategies recently adopted by law enforcement. In long-range familial search, investigators seek to identify the source of a crime-scene sample by identifying relatives of the sample in a genetic genealogy database that allows uploads. Searching in SNP-based genealogy databases allows the detection of much more distant relationships than does familial searching in traditional forensic microsatellite datasets (Rohlfs et al., 2012), vastly increasing the number of people detectable by familial search (Erlich et al., 2018; Edge and Coop, 2019). At this writing, both GEDmatch and FamilyTreeDNA have been searched in this way. Long-range familial search raises a range of privacy concerns (Court, 2018; Ram et al., 2018; Kennett, 2019; Scudder et al., 2019). One response from advocates of long-range search has been to note that "raw genetic data are not disclosed to law enforcement...Search results display only the length and chromosomal location of shared DNA blocks" (Greytak et al., 2018). However, the methods we describe here illustrate that there are several ways to reveal users' raw genetic data on the basis of the locations of shared DNA blocks. Because companies that work with law enforcement on long-range familial searching—including Parabon Nanolabs and Bode Technology (Kennett, 2019)—now routinely upload tens of datasets to genetic genealogy databases, they may be accidentally accumulating information that would allow them to reconstruct many people's genotypes.

Data breaches via IBS tiling, IBS probing, and IBS baiting are preventable. We have identified a set of strategies that genetic genealogy services could adopt to protect their genotype data from IBS-based attacks. We list these strategies here (also summarized in Table 2):

1. **Require uploaded files to include cryptographic signatures identifying their source.** This recommendation was initially made by Erlich et al. (2018). Under this suggestion, DTC genetics services would cryptographically sign the genetic data files they provide to users. Upload services might then check for a signature from an approved DTC service on each uploaded dataset, blocking datasets from upload otherwise. An alternative procedure that would accomplish the same goal would be for the DTC entities to exchange data directly at the user's request (Ney et al., 2018). Such a procedure would allow upload services to know the source of the files they analyze and to disallow uploaded datasets produced by non-approved entities and user-modified datasets. All the methods we describe require the upload of multiple genetic datasets. As such, requiring cryptographic signatures would force the adversary to have multiple biological samples analyzed by a DTC service in order to implement any of our procedures, and IBS probing and IBS baiting would require synthetic samples, which are much harder to produce than fake datasets. Another benefit of this

Strategy	Prevents IBS tiling	Prevents IBS probing	Prevents IBS baiting
Require cryptographic signature from genotyping service	Yes	Yes	Yes
Restrict reporting of IBS to long segments (e.g. >8 cM)	Partially	Partially	Weakly
Report number and lengths of IBS segments but not locations	Yes	No	Partially
Block homozygous uploads	Partially	No	No
Report small number of matching individuals per kit	Partially	Partially	Partially
Disallow matching between arbitrary kits	Partially	Partially	Partially
Block uploads of publicly available genomes	Partially	No	No
Block uploads with evidence of IBS-inert segments	No	Yes	No
Block uploads with long runs of heterozygosity	No	No	Partially
Use phase-aware methods for IBS detection	No	No	Yes

Table 2: Potential countermeasures against the methods of attack outlined here, with their likely effectiveness against IBS tiling, IBS probing, and IBS baiting.

approach is that it would protect research participants against being reidentified using DTC genetic genealogy services (Erlich et al., 2018). A disadvantage of this strategy is that it requires the cooperation of several distinct DTC services.

2. **Restrict reporting of IBS to long segments.** Reporting short IBS segments increases the typical coverage of IBS tiling (Figure 2) and IBS probing (3), as well as the efficiency of IBS baiting. Very short blocks may be of little practical utility for genetic genealogy (Huff et al., 2011). Reporting only segments longer than 8 cM would substantially limit IBS tiling attacks. A partially effective variant of this strategy is to report short segments only for pairs of people who share at least one long segment (Figure S2).

3. **Do not report locations of IBS segments.** Another tactic for preventing IBS tiling is not to report chromosomal locations at all. If chromosomal locations are not reported, IBS tiling as we have described it becomes impossible.

4. **Block uploads of genomes with excessive homozygosity.** IBS tiling is especially informative if genotypes that are homozygous for phased haplotypes are uploaded, so blocking genomes with excessive homozygosity presents a barrier to IBS tiling attacks. However, runs of homozygosity occur naturally (Pemberton et al., 2012), and allowing for naturally occurring patterns of homozygosity would leave a loophole for an adversary who could upload many genotypes, using including homozygous regions and using only those for tiling.

5. **Report only a small number of putative relatives per uploaded kit.** Reporting only the closest relatives (say the ≈ 50 closest relatives) of an uploaded kit would decrease the

efficiency of all the methods we describe here. Only a small number of people could have their privacy compromised by each upload.

6. **Disallow arbitrary matching between kits.** Some services allow searches for IBS between any pair of individuals in the database. Allowing such searches makes all potential IBS attacks easier.

7. **Block uploads of publicly available genomes.** There are now thousands of genomes available for public download, and these publicly available genomes can be used for IBS tiling. Genetic genealogy databases could include publicly available genomes (potentially without allowing them to be returned as IBS matches for typical users) and flag accounts that upload them. This strategy would go some distance toward blocking IBS tiling, but it could be thwarted in several ways, for example by uploading genetic datasets produced by splicing together haplotypes from publicly available genomes.

8. **Block uploads with evidence of IBS-inert segments.** IBS-inert segments—i.e. false genetic segments designed to be unlikely to be IBS with anyone in the database—are key to IBS probing. Some methods for constructing IBS-inert segments are easy to identify, but others may not be. If a database is large enough, genomes with IBS-inert segments could be identified by looking for genomes that have much less apparent IBS with other database members than might be expected.

9. **Block uploads with long runs of heterozygosity.** Long runs of heterozygosity do not arise naturally but are key to the IBS baiting approaches we describe here. Blocking genomes with long runs of heterozygosity—or alternatively, blocking genomes that have much more apparent IBS with a range of other database members than expected—would hamper IBS baiting. However, this countermeasure might be hard to apply to a small-scale IBS baiting attack, where only one or a few short runs of heterozygosity might be necessary.

10. **Use phase-aware methods for IBS detection.** Although calling IBS by looking for long segments without incompatible homozygous genotypes scales well to large datasets, such methods are easy to trick, allowing IBS baiting approaches. In addition to allowing IBS estimation methods that are harder to trick, faked samples may stand out as unusual during the process of phasing, raising more opportunities for quality-control checks.

All of these suggestions assume that genealogy services will maintain raw genetic data for people in their database. Another possibility would be for individual people instead to upload an encrypted version of their genetic data, with relative matching performed on the encrypted datasets, as has been suggested previously (He et al., 2014). Some of these suggestions limit the potential uses of genetic genealogy data, and users will vary in the degree to which they value these potential uses and in the degree to which they want to protect their genetic information.

We have focused on genetic genealogy databases that allow uploads because at this writing, it is straightforward to download publicly available genetic datasets and to produce fake genetic datasets for upload. In principle, however, another way to perform attacks like the ones we describe would be to use biological samples. For example, a group of people willing to share their genetic data with each other could collaborate to perform IBS tiling by sending actual biological samples for genotyping. Even IBS probing and IBS baiting could be performed with biological samples by adversaries who could synthesize the samples. Though synthesizing such samples is technically challenging now, it may become easier in the future. Such methods could present opportunities to attack databases that do not allow uploads, such as the large databases maintained by Ancestry (>14 million) and 23andMe (>9 million) (Regalado, 2019). They would also thwart the countermeasure of requiring uploaded datasets to include an cryptographic signature indicating their source.

The IBS-based privacy attacks we describe here add to a growing set of threats to genetic privacy (Homer et al., 2008; Nyholt et al., 2009; Im et al., 2012; Gymrek et al., 2013; Humbert et al., 2015; Shringarpure and Bustamante, 2015; Edge et al., 2017; Ayday and Humbert, 2017; Kim et al., 2018; Erlich et al., 2018). A person's genotype includes sensitive health information that might be used for discrimination, particularly as our ability to genetically predict traits and disease predispositions will likely improve over the coming years. Further, genetic privacy concerns not only the person whose genotypes are directly revealed but also their relatives whose genotypes may be revealed indirectly (Humbert et al., 2013). Though many forms of genetic discrimination are prohibited legally, rules vary between countries and states. For example, in the United States, the Genetic Information Nondiscrimination Act (GINA) protects against genetic discrimination in the provision of health insurance but does not explicitly disallow genetic discrimination in the provision of life insurance, disability insurance, or long-term care insurance (Bélisle-Pipon et al., 2019). In addition to measures for protecting genetic privacy in the short term, there is a need for more complete frameworks governing the circumstances under which genetic data can be used (Clayton et al., 2019).

4 Methods

4.1 Data assembly

We performed IBS tiling with publicly available genoytpes from 872 people of European ancestries. Of these 872 genotypes, 503 came from the EUR subset of phase 3 of the 1000 Genomes project (1000 Genomes Project Consortium, 2012), downloaded from `ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/`. The EUR subset includes the following population codes and numbers of people: CEU (Utah residents with Northern and Western European Ancestry, 99 people), FIN (Finnish in Finland, 99 people), GBR (British in England and Scotland, 91 people), IBS (Iberian Population in Spain, 107 people), TSI (Toscani in Italia, 107 people).

The remaining 369 were selected from samples typed on the Human Origins SNP array (Patterson et al., 2012), including 142 genotypes from the Human Genome Diversity Project (Cann et al., 2002). Specifically, we downloaded the Human Origins data from `https://reich.hms.harvard.edu/downloadable-genotypes-present-day-and-ancient-dna-data-compiled-published-papers`, using the 1240K+HO dataset, version 37.2. The 372 selected people were all contemporary samples chosen according to population labels. We also excluded people from the Human Origins dataset if they appeared in the 1000 Genomes dataset. The populations used for selecting data, along with the number of participants included after excluding 1000 Genomes samples, were as follows: "Adygei" (16), "Albanian" (6), "Basque" (29), "Belarusian" (10), "Bulgarian" (10), "Croatian" (10), "Czech" (10), "English" (0), "Estonian" (10), "Finnish" (0), "French" (61), "Greek" (20), "Hungarian" (20), "Icelandic" (12), "Italian_North" (20), "Italian_South" (4), "Lithuanian" (10), "Maltese" (8), "Mordovian" (10), "Norwegian" (11), "Orcadian" (13), "Romanian" (10), "Russian" (22), "Sardinian" (27), "Scottish" (0), "Sicilian" (11), "Spanish" (0), "Spanish_North" (0), and "Ukrainian" (9). The populations with 0 people included are those for which all the samples in the Human Origins dataset are included in the 1000 Genomes phase 3 panel.

We down-sampled the sequence data from the 1000 Genomes project to include only sites typed by the Human Origins chip. Of the 597,573 SNPs included in the Human Origins dataset, 558,257 sites appeared at the same position in the 1000 Genomes dataset, 557,999 of which appear as biallelic SNPs. For 546,530 of these, both the SNP identifier and position match in 1000 Genomes, and for 544,139 of them, the alleles agreed as well. We merged the dataset at the set of 544,139 SNPs at which SNP identifiers, positions, and alleles matched between the Human Origins and 1000 Genomes datasets.

We used vcftools (Danecek et al., 2011), bcftools (Li, 2011), PLINK (Purcell et al., 2007), and EIGENSOFT Price et al. (2006) to create the merged file. The script used to create it is available at `github.com/mdedge/IBS_privacy/`, and the merged data file is available at `https://doi.org/10.25338/B8X619`.

4.2 Phasing, IBS calling, and IBS tiling

We phased the combined dataset using Beagle 5.0 Browning and Browning (2007) using the default settings and genetic maps for each chromosome. We used Refined IBD software (Browning and Browning, 2013) to identify IBS segments, retaining segments of at least .8 centiMorgans (cM) with LOD scores >1. We also used Germline (Gusev et al., 2009) to identify IBS segments under alternative parameters, shown in the supplement. The resulting IBS segments were analyzed using the GenomicRanges package (Lawrence et al., 2013) in R (R Core Team, 2013). Scripts used for phasing, IBS calling, and IBS tiling are available at `github.com/mdedge/IBS_privacy/`.

4.3 IBS probing

To generate IBS-inert genotypes for IBS probing in Figure 3, we computed allele frequencies within the set of 872 Europeans for chromosome 19. Allele frequencies less than 10% were changed to 10%, and then alleles were sampled at one minus their frequency. This strategy generates genetic data that look quite unlike real data but that are unlikely to return IBS matches anywhere. An adversary attempting IBS probing in a real database would need to tailor the approach to the quality control and IBS calling methods used by the database.

After inert genotypes were produced, we stitched them with real phased genotypes from windows around GRCh position 45411941 on chromosome 19, the site of SNP rs429358. SNP rs429358 is in the APOE locus; if a haplotype has a C at rs429358 and a C at nearby SNP rs7412, then that haplotype is said to harbor the APO-$\epsilon4$ allele, which confers risk for Alzheimer's disease Corder et al. (1993). rs429358 is not genotyped on the Human Origins chip, but it is included on recent chips used by both Ancestry and 23andMe. To simulate probing with a 1cM threshold for matching, we pulled real data from a region of 1.9cM around the site, and to simulate probing with a 3cM threshold, we pulled real data from a region of 5.9cM around the site. Distances in cM were computed by linear interpolation from a genetic map in GRCh37 coordinates. Scripts used to generate Figure 3 are available at `github.com/mdedge/IBS_privacy/`.

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Supplementary Figures

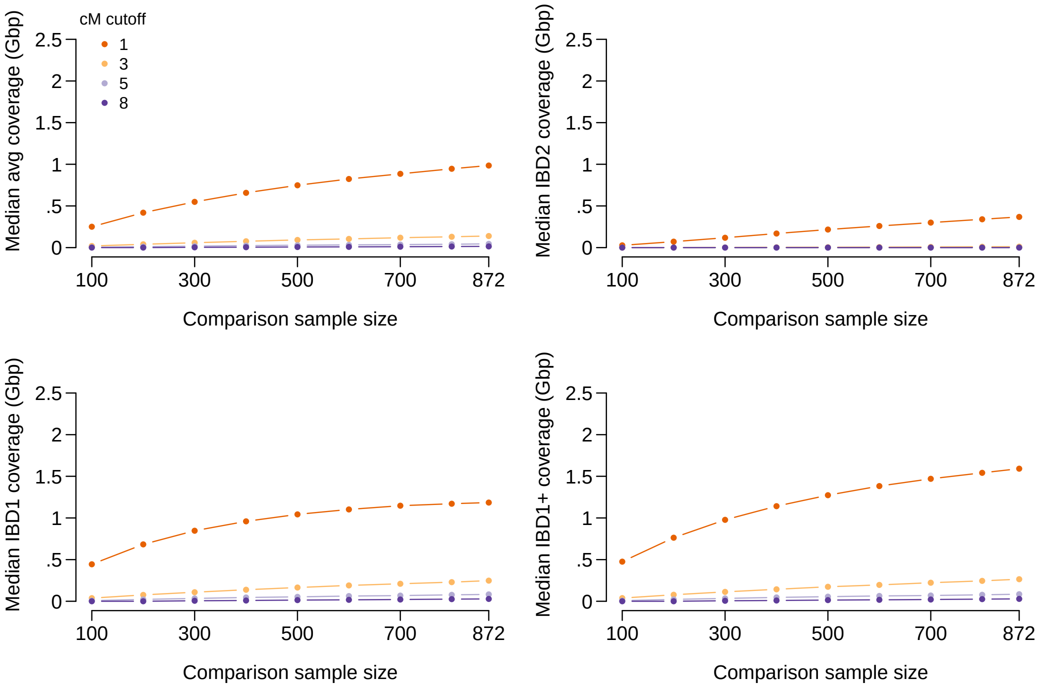

Figure S1: Tiling performance with IBS segments that are unlikely to be IBD filtered out. Conventions are the same as in Figure 2; the difference is that now only IBS segments that represent likely IBD (LOD score > 3) are included. As expected, the amount of tiling possible is reduced when the LOD score threshold is increased, particularly when segments as short as 1 cM are allowed. However, tiling still reveals a substantial amount of information about target genotypes. Using a comparison sample of 871, and including all called IBS segments >1 cM, the median person has an average of 35% of the maximum length of 2.8 Gbp covered by IBD segments with LOD >3, and has at least one chromosome covered for approximately 57% of the genome. If only segments >3 cM are included, then averaging across the two chromosomes, median coverage is 5.0%, and the median proportion for which at least one chromosome is covered is 9.5%. As before, the percentage of the genome recoverable by tiling varies among people, and some people still have large proportions of their genetic data recoverable by tiling. With a LOD score threshold of 3, the top 10% of people have at least 58% of their total genotype information covered by IBD tiles, including one or more alleles at sites in at least 81% of the genome covered by IBD tiles.

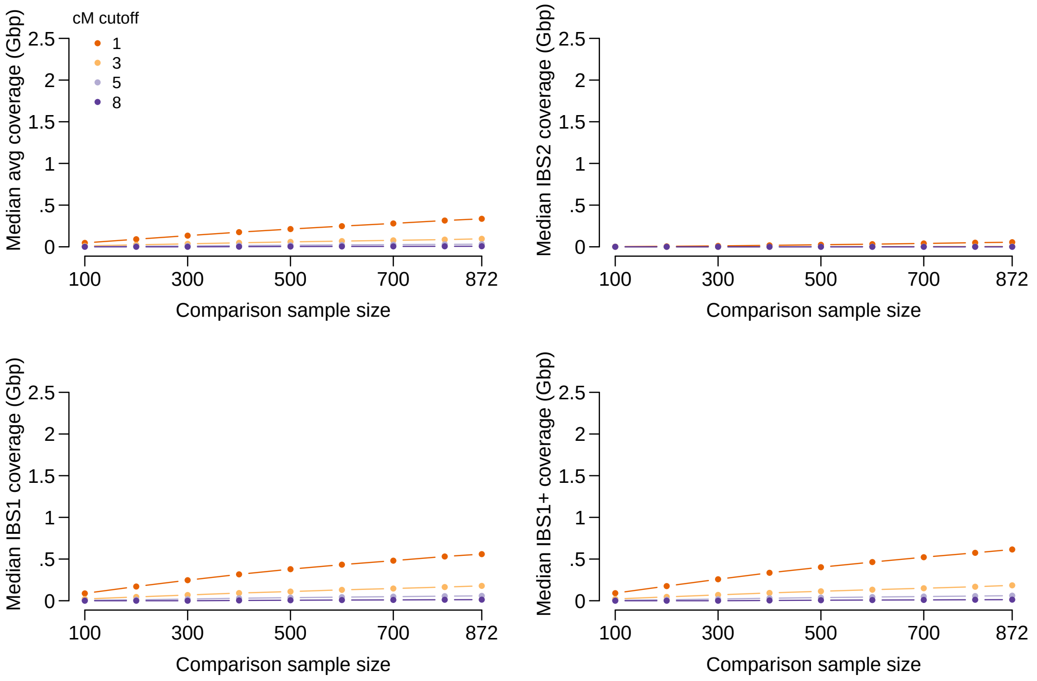

Figure S2: IBS tiling performance, limiting to comparison samples who share at least 1 IBS segment of 8 cM or more with the target. Conventions are the same as in Figure 2. Some DTC genetics companies use a two-step approach for reporting IBS information to users. For example, at this writing, MyHeritage identifies people who are likely matches of a given user as all those who share an apparent IBD segment of at least 8 cM with the user. However, once matches are identified, inferred IBD segments down to a minimum length of 6 cM are reported to the user (see Table 1). Similarly, FamilyTreeDNA only reports matching segments for pairs of people who pass a sharing threshold, and for those pairs of individuals they report all matches down to 1cM. As expected, reporting only IBS segments for pairs of people who share at least one long IBS segment (>8 cM) substantially reduces but does not eliminate the effectiveness of IBS tiling. With 872 comparison samples, the median person has approximately 12% of their genome covered by IBS tiles of 1 cM or more (averaged across both chromosomes) and at least one chromosome covered for 21% of the genome. People in the top 10% of IBS tiling coverage have 44% of their genome length recoverable by tiling (averaging across both chromosomes), with at least one chromosome tiled over more than 67% of the genome. Importantly, the practice of requiring at least one long IBS match in order to report any IBS segments will not reduce the effectiveness of IBS tiling if phase-unaware methods are used for calling IBS. In that case, the attacker could simply insert a long run of heterozygous sites in each of the genomic datasets uploaded, causing an apparent long run of IBS with every user in the database (see section 2.3). After getting "in the door" with a long run of heterozygous sites, the attacker could then use tiling to find out about the rest of the genome.

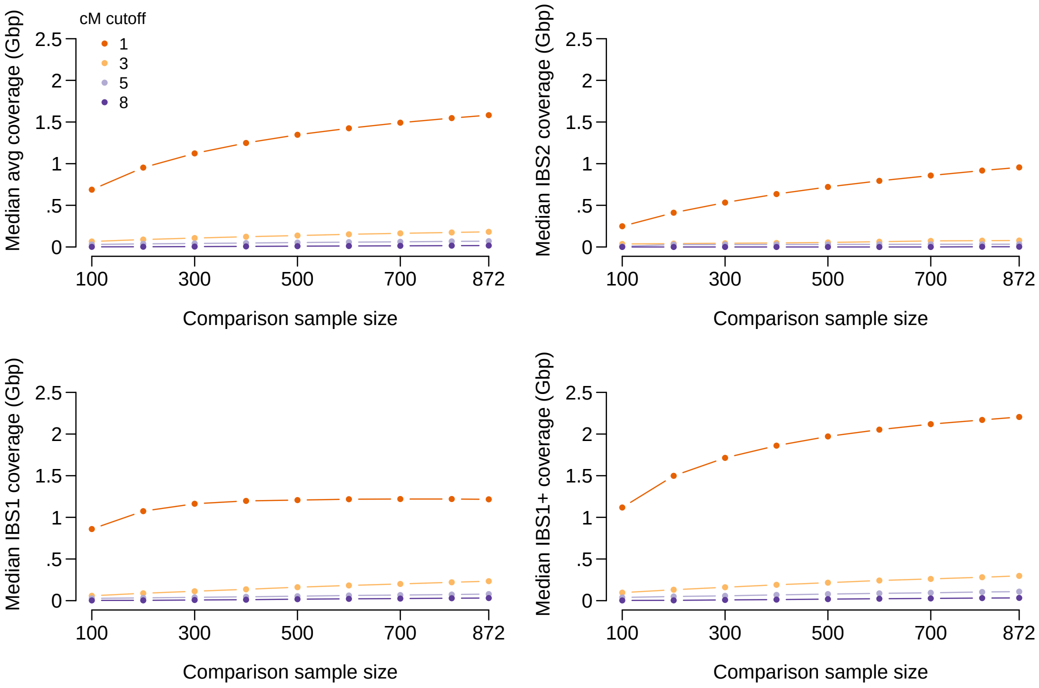

Figure S3: IBS tiling performance when genotype phasing switches are disallowed. Conventions are the same as in the Figure 2. We called IBS segments using Germline (Gusev et al., 2009), using the haploid flag to find IBS segments within the phased chromosomes produced by Beagle. We also set the err_hom argument to zero, set the bits argument to 32 to increase sensitivity for short segments, used the w_extend flag to extend segments beyond the slices produced by Germline, and set the minimum IBS segment length to 1cM. The amount of tiling possible is reduced somewhat when phase switches are disallowed. However, tiling still reveals substantial information about target genotypes. Using a comparison sample of 871, and including all called IBS segments >1 cM, the median person has an average of 57% of the maximum length of 2.8 Gbp covered by IBS segments, and has at least one chromosome covered for approximately 79% of the genome. If only segments >3 cM are included, then averaging across the two chromosomes, median coverage is 6.5%, and the median proportion for which at least one chromosome is covered is 11%. The top 10% of people have at least 73% of their genomes covered by IBS tiles of 1 cM or more, including one or more alleles at sites in at least 91% of the genome covered by IBS tiles.

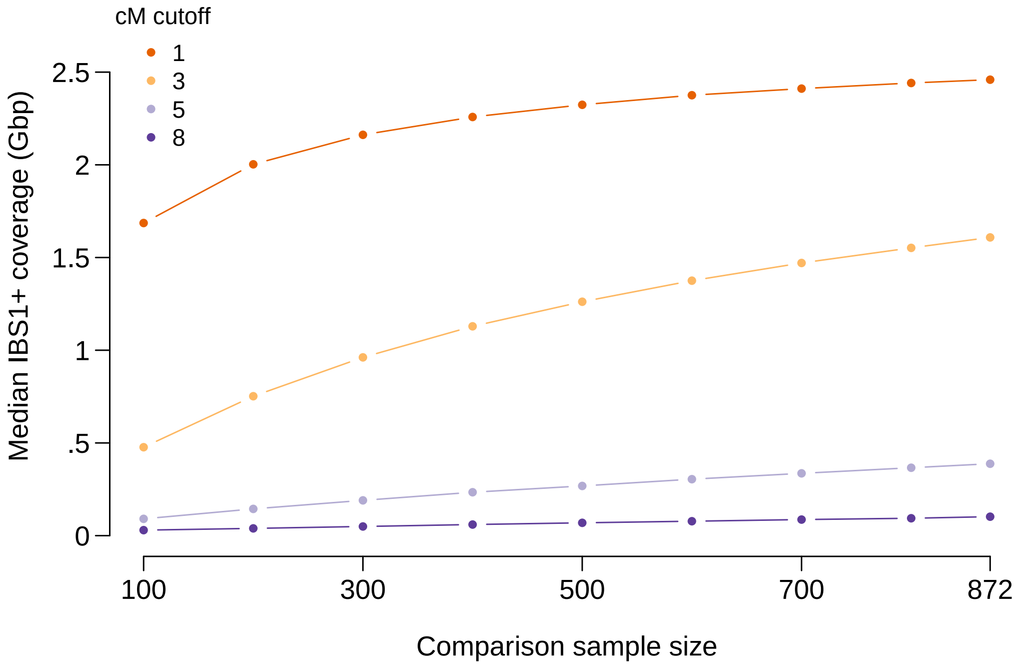

Figure S4: IBS tiling performance using a phase-unaware method to call IBS segments. Conventions are the same as in the bottom-right panel of Figure 2. We called IBS segments using Germline (Gusev et al., 2009), using the g_extend flag to find segments without incompatible homozygous genotypes. This procedure extends IBS segments irrespective of phasing, but it does not distinguish which haplotype is covered by IBS. We set the err_hom argument to zero to disallow incompatible homozygous sites inside an IBS segment, used the w_extend flag to extend segments beyond the slices produced by Germline, and set the minimum IBS segment length to 1cM. All other arguments were kept at their default values. Calling IBS without respect to genotype phase returns many IBS segments, but less can be learned about each segment via tiling than if haplotype phase is respected. For the median person, with a comparison sample of 871, and for at least one of the two haplotypes, 88% of the genome is covered by IBS tiles of at least 1 cM, 58% is covered by IBS tiles of at least 3 cM, 14% is covered by IBS tiles of at least 5 cM, and 3.6% is covered by IBS tiles of at least 8 cM.

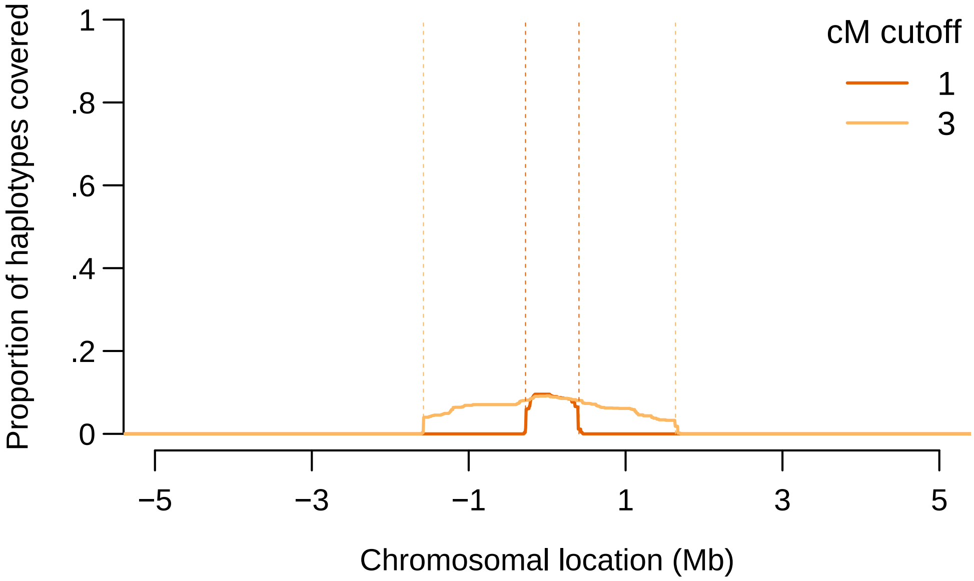

Figure S5: A demonstration of the IBD probing method around position 45411941 on chromosome 19 (GRCh37 coordinates), in the APOE locus. Conventions are the same as in Figure 3; the difference is that only IBS segments with a LOD score >3 for IBD are included. When IBD probing is performed with a 1-cM threshold, 9.6% of haplotypes had a match among the probes constructed from the other 871 people in the dataset. With a 3-cM threshold, 9.2% of haplotypes had a match.

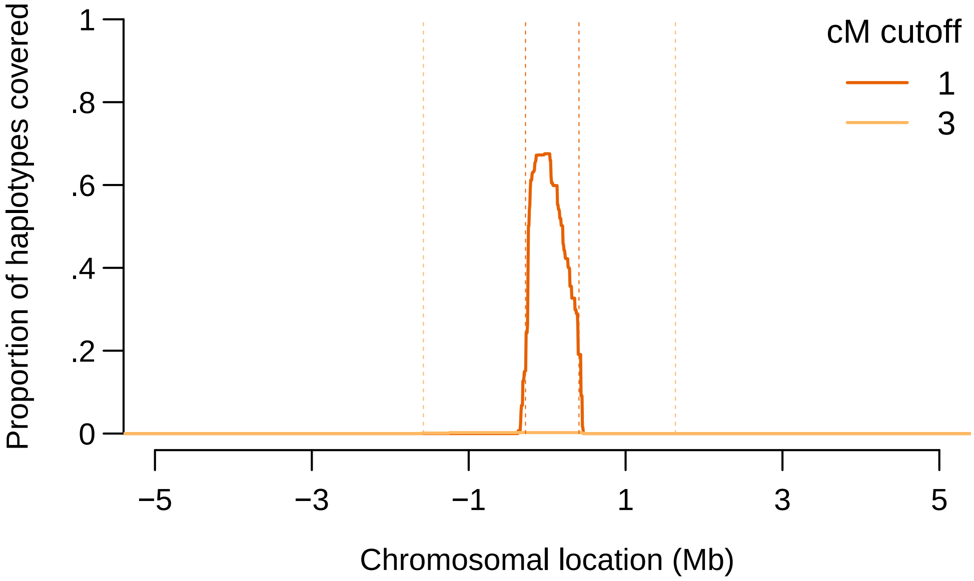

Figure S6: A demonstration of the IBS probing method around position 45411941 on chromosome 19 (GRCh37 coordinates), in the APOE locus. Conventions are the same as in Figure 3; the difference is that IBS calling was performed by Germline (Gusev et al., 2009) in haploid mode, meaning that phasing switches are disallowed. We set the err_hom argument to zero, we used the w_extend flag to extend segments beyond the slices produced by Germline, and we set the minimum IBS segment length to 1cM. All other arguments were kept at their default values. When IBS probing is performed with a 1-cM threshold, 67.5% of haplotypes had a match among the probes constructed from the other 871 people in the dataset. With a 3-cM threshold, 0.2% of haplotypes had a match.