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PAGEANT: personal access to genome and analysis of natural traits

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ABSTRACT

GWASs have identified numerous genetic variants associated with a wide variety of diseases, yet despite the wide availability of genetic testing the insights that would enhance the interpretability of these results are not widely available to members of the public. As a proof of concept and demonstration of technological feasibility, we developed PAGEANT (Personal Access to Genome & Analysis of Natural Traits), usable through Graphical User Interface or command line-based version, aiming to serve as a protocol and prototype that guides the overarching design of genetic reporting tools. PAGEANT is structured across five core modules, summarized by five Qs: (i) quality assurance of the genetic data; (ii) qualitative assessment of genetic characteristics; (iii) quantitative assessment of health risk susceptibility based on polygenic risk scores and population reference; (iv) query of third-party variant databases (e.g. ClinVAR and PharmGKB) and (v) quick Response code of genetic variants of interest. Literature review was conducted to compare PAGEANT with academic and industry tools. For 2504 genomes made publicly available through the 1000 Genomes Project, we derived their genomic characteristics for a suite of qualitative and quantitative traits. One exemplary trait is susceptibility to COVID-19, based on the most up-to-date scientific findings reported.

INTRODUCTION

The start of the millennium was marked by a significant achievement of human health research—the completion of the draft Human Genome Project. Over the past two decades, millions of human genomes have been sequenced and even many more have been genotyped. The journey of human genomics could be summarized by 4Ps: starting from an international human genome 'project' to numerous scientific 'publications', human genetic research is now serving 'patients' and eventually all 'people'.

Academia has thus far been the driving force for discovering genetic loci associated with complex traits, delivering thousands of genome-wide association studies (GWASs), and reporting millions of genetic loci plausibly associated with various diseases and health conditions. GWASs have grown from hundreds of participants to over a million (1), spanning a wide range of health phenotypes. Polygenic Risk Scores (PRS) based on GWAS results can incorporate millions of genetic variants to accurately predict individual risk of health conditions, with some offering superior predictive performance compared to established risk factors (2,3). The concept of 'big data' for health is finally becoming actionable, in that genetic variation may have diagnostic or therapeutic implications.

A comprehensive review of the literature on well-studied common diseases/traits where PRS showed clinical value was recently conducted by Lewis and Vassos (4). The predictive accuracy of the PRS has already demonstrated for common diseases including type 2 diabetes (5) and coronary heart disease (6). Also, using data from the large-scale UK Biobank study (7), researchers from the United States,

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United Kingdom (8) and Pacific Islands (9) have generated GWAS results for thousands of traits and billions of data points; these findings provide new insights into disease risk (10). However, the public lack the means to avail such data for interpretation of their own genomes. There is therefore a need for the design and development of user-friendly systems for delivering personalized genomic information, both for disease treatment and prevention, considering individual genetic variation, lifestyle, and environmental characteristics (11).

Several direct-to-consumer (DTC) companies offer genetic testing and reporting over the counter and online, with millions of users now having had their DNA assayed and received genetic reports (12). Genetic testing is a key area for US government regulation agencies. As of October 2021, the US National Institute of Health (NIH) National Center for Biotechnology Information (NCBI) Genetic Testing Registry contains over 70 000 genetic tests for over 18 000 conditions (13). Also, the US Food and Drug Administration (FDA) has over 400 entries for pharmacogenomic biomarkers used in drug labeling and published a list of Direct-To-Consumer (DTC) tests with marketing authorization (https://www.fda.gov/medical-devices/in-vitro-diagnostics/direct-consumer-tests#list). Nevertheless, DTC genetic testing is under strict government regulation, and several important ethical concerns remain (14). Concerns include possible psychological harm (15), lack of professional genetic counselling (16), lack of data protection (17) and lack of validity and clinical utility of test results (18).

Under the guidance of ethical principles especially related to genetic data confidentiality, we developed PAGEANT (Personal Access to Genome & Analysis of Natural Traits), a self-completion genetic reporting tool for individuals with personal genomic data. PAGEANT follows five core philosophies, summarized by the five letters for nucleic acids (A, C, G, T, U): (i) Academic quality and standards. State-of-the-art algorithms incorporate millions of genetic variants to calculate individual Polygenic Risk Score (PRS); (ii) **C**onfidential data run locally, without the need to send genomic data to cloud servers; (iii) **G**eneralizable architecture and algorithm, where our 'five-Q' design could easily grow from the basic version for dozens of traits to hundreds and thousands of traits; (iv) **T**ransparent source code for all underlying programming scripts; (v) **U**ser-centric, as users have full control to add or remove certain traits into or from a genetic report.

PAGEANT aims to provide proof of concept for a scientifically driven architecture with a user-friendly interface, offering a technologically feasible approach to allow users to understand their genetic traits and predictive value of an individual's genomic variation. The overreaching goal of PAGEANT is to offer the public a freely accessible platform to analyze and interpret their own genome, reliably and conveniently, thus fostering an increased awareness of the information contained in personal genomic data.

METHODS

Review and comparison with existing tools

With the aim of contextualizing PAGEANT in the present setting, we performed an extensive literature search on both PubMed and Google using the keywords: 'personalized genome', 'third-party interpretation', 'genome interpretation', 'genome', 'genetic testing' and 'risk prediction' applying the following algorithm: (genome interpretation OR genome) AND (third-party interpretation) AND (genetic testing OR risk prediction). The identification of eligible studies was not restricted to English language. Studies references were also analyzed to find any study not available from the electronic databases. We also determined whether each of the identified tools are still functional and available on the web until July 2021.

Overarching design of the user interface

PAGEANT is an open-source, customizable platform with a version suitable for non-technical users. The basic version of PAGEANT has five modules, summarized by five Qs, described below.

(1) *Quality control report of genetic data*. To our knowledge, PAGEANT is the only genetic reporting tool that first reports genotype quality before reporting genotype-derived results. This step is especially important for DTC users, to ensure quality control. PAGEANT generates a genotype quality control (QC) report for the input personal genome and for thousands of genomes used in the reference panel later used for calculation of the PRS. PAGEANT takes as input a variant call format (VCF) file, generated using a variety of genotyping platforms, such as whole-genome sequencing or Single Nucleotide Polymorphism (SNP) array. Using PLINK (19), PAGEANT determines fundamentals QC metrics such as chromosome-level of heterozygosity and genetically derived sex. Principal Component Analysis (PCA) is performed using PLINK (19) on independent SNPs ($r^2 \leq 0.2$). Uniform Manifold Approximation and Projection (UMAP) analysis is conducted on the raw genetic data using standard UMAP python package.

(2) *Qualitative assessment of genetic characteristics of absolute or relatively high certainty*. We broadly divided the traits into qualitative and quantitative traits. Qualitative traits are categorical such as YES/NO or Presence/Absence or categorical such as blood type (A, B, AB, O). The determination of qualitative traits is straightforward with a definitive outcome obtained from the presence of target variants. Examples include tagging a particular functional haplotype of broad clinical relevance (such as ABO blood type, *APOE* genotype, *FTO* flagship SNP rs9939609, etc.).

(3) *Quantitative assessment of health risk susceptibility based on PRS*. PAGEANT is pre-installed with a small number of complex traits that have high disease burden and strong evidence of genetic risk prediction. We used GWAS summary results from UK Biobank (UKB, http://www.nealelab.is/uk-biobank) and BioBank Japan (BBJ, http://jenger.riken.jp/en/result). The PRS is based on an allelic scoring system involving one or more SNPs, and it is implemented through PLINK's '–score' function. For each trait, there is a score reference file that includes the list of SNPs and their weights (usually association beta values). This file is usually extracted from publications for each corresponding

trait. When the raw GWAS summary statistics file is available, PAGEANT could also automatically generate the score reference file through PLINK's clumping function (19). The default parameters for clumping could be updated on the GUI interface. To allow users to interpret their own PRS in the context of a large population, PAGEANT uses the specified list of SNPs and statistical models to calculate PRS for the provided population reference, in addition to calculating PRS for individuals. The 1000 Genomes Project (G1K) genetic data (https://www.internationalgenome.org/data/) (20) are the foundation for most GWAS and PRS studies, and this is used as the default reference panel. PAGEANT defines three risk categories based on the position of the personal genome across the PRS distribution (<25% Low risk, 25–75% Normal, >75% high risk).

(4) *Query of third-party variants databases such as ClinVAR* (21) *and PharmGKB* (22). This aims to increase PAGEANT's generalizability. With increasing interest in precision health and guidelines for drug usage, SNPs that predict clinical pathogenicity and pharmacogenomic relevance are increasingly incorporated into genotyping array panels. At the same time, SNPs with detailed annotations are added into such databases constantly. This module establishes technical standards and facilitates a diverse range of genetic interpretation tools.

(5) Quick Response (QR) code generation for tagging individual genomes, guaranteeing personal privacy and quick retrieval of the PAGEANT genetic report. Our group previously developed a SNP panel and an online tool for checking genotype concordance through comparing QR codes (23). In that work we identified 80 'fingerprinting' SNPs that could be used to uniquely identify a person. We subsequently implemented a web-based tool to convert the genotype of those 80 SNPs into a QR code, so that users could use that QR code as a genetic ID for quick concordance check. Here, the QR code module in PAGEANT uses the same 80 SNPs as an example, to illustrate how a user could conveniently scan a list of SNPs coded and encrypted in a QR code to extract his personal genomic data for downstream usage.

A more detailed technical description of the core elements (five Qs), including the PRS calculations, is reported in the Wiki section of PAGEANT (https://github.com/jielab/pageant/wiki).

The selected traits used in the default version of PAGEANT aim to ideally balance the 'quality/meaning' of both qualitative and quantitative traits according to their clinical (e.g. *ABO*, *APOE*, Age Related Macular Degeneration, Breast Cancer) and mundane relevance (e.g. Alcohol Flush, Altruism, Marital Satisfaction). By doing so, we are providing the non-technical user with a general overview of the possible information obtainable from a DTC genetic report, ranging from very 'serious' traits (e.g. Cancers, COVID) to 'very exotic' traits (e.g. marital satisfaction, altruism).

Technical implementation

The tool is written using Python v3; the *Pandas* module was used to read, clean, and analyze various data. The *Matplotlib* module was used for plotting. The *PyQt5* module was used for API related functionality (along with specific classes linked to Qt C++, it facilitates further graphical applications). The *Jinja2* module was used to generate the HTML report. Finally, we used the *Pyinstaller* module to organize core scripts and all dependencies into a single executable file, without the need to construct the running environment.

We also embedded PLINK (19) to convert and filter the genotype data, to perform QC and to calculate PRS. In our default version, we also embedded two widely used genetic databases: ClinVar (21) and PharmGKB (22).

Finally, for the fifth Q (QR code), we used existing python packages 'qrcode' and 'pyzbar' for encoding/decoding and 'rsa' and 'pyDes' for encryption/decryption. The encryption/decryption is based on an asymmetric cryptography algorithm.

The technical anatomy of the five Qs, including Python functions/subfunctions along with the core codes used, is reported as Supplementary Figures S1–S4.

Application Programming Interfaces (APIs) for projecting personal genome on population reference genomes and for generating QR code, based on a SNP list and public key, were written from scratch with commonly used python libraries. An API for adding rsID was modeled on a similar python script of Pheweb (24), with the added flexibility to specify the REF versus ALT alleles. This API will foreseeably be replaced by standard genomic tools (i.e. bcftools) once the VCF format is widely used for GWAS (25). The source code and example command line usage for all three APIs are presented on PAGEANT GitHub page (https://github.com/jielab/pageant).

RESULTS

Review and comparison with existing tools

Through the literature search we identified a structured content analysis of 23 third-party interpretation tools conducted by Nelson and Fullerton published in 2018 (26), on which we decided to build our review and comparative analysis. Thus, we searched for tools that were made available to the public since the end of their review period (December 2016), identifying five additional third-party interpretation tools, namely Allelica, CodeGenEU, GenePlaza, Impute.me and Self Decode (Table 1).t

Among all the 28 tools that we reviewed, four (Interpretome, Anabolic Genes, GENETIConcept and GeneKnot) were deactivated, with AnabolicGenes and GENETIConcept being incorporated into a new company, named 'Oh My Genes', which appears inactive (Table 1). Since the main aim of PAGEANT is to provide an open-source, customizable platform for determining individual genetic-based risk profiles, based on reliable and transparent resource provided by the academic field, we focused our attention on tools available free of charge by academic-based providers.

Three tools categorised as academic-based providers by Nelson and Fullerton (26) were not considered as such in

Table 1. DTC genetic testing interpretation tools. For each identified tool we reported the developer type, country, website link and their status (active vs. deactivated) in July 2021. NA = not available

Name	Developer type	Country	Web-site link	Status
Impute.me	Academic	Denmark	https://www.impute.me/	Active
Infinome	Academic	USA	https://www.infino.me/	Active
Interpretome	Academic	USA	NA	Deactivated
openSNP	Academic	Germany	https://opensnp.org/	Active
Allelica	Company	Italy	https://www.allelica.com/	Active
Anabolic Genes	Company	France	http://www.anabolicgenes.com/	Deactivated
Athletigen	Company	Canada	https://athletigen.com/	Active
CodeGenEU	Company	Europe (Not Specified)	https://codegen.eu/	Active
DNA Doctor	Company	USA	http://www.biostatushealth.com/dnadoctor/	Active
DNA Tribes	Company	USA	https://dnatribes.com/	Active
DNA.land	Company	USA	https://dna.land/	Active
DNAFit	Company	UK	https://www.dnafit.com	Active
Enlis Genome Personal	Company	USA	https://www.enlis.com/personal_edition.html	Active
Family Tree DNA	Company	USA	https://www.familytreedna.com	Active
GEDMatch	Company	USA	https://www.gedmatch.com/	Active
GenePlaza	Company	France	https://www.geneplaza.com/	Active
Genetic Genie	Company	USA	https://geneticgenie.org/	Active
GENETIConcept/Oh My Genes	Company	France	http://fr.geneticoncept.com/index.html	Deactivated
Golden Helix Genome Browser	Company	USA	https://www.goldenhelix.com/products/GenomeBrowse/	Active
GPS Origins	Company	UK	https://www.ibdna.com/tests/gps-origins/	Active
Livewello	Company	USA	https://livewello.com/	Active
NutraHacker	Company	USA	https://www.nutrahacker.com/	Active
Promethase	Company	Israel	https://promethease.com/	Active
Self Decode	Company	UK	https://selfdecode.com/	Active
WeGene	Company	China	https://www.wegene.com/en/	Active
David Pike's utilities	Non-specialist	Canada	https://www.math.mun.ca/~dapike/FF23utils/	Active
GeneKnot	Non-specialist	NA	NA	Deactivated
James Lick Haplogroup Analysis	Non-specialist	NA	https://dna.jameslick.com/mthap/	Active

the current review. Promethase, a tool developed by the SNPedia team, requires a fee to pay (minimum $12) according to the number of reports requested by the user. Likewise, DNA.land (27), recently transitioned from an academic research project to a for-profit company, and the source code is not publicly available. Infino.me requires health (weight and blood pressure) and physical activity measures obtained from personally wearable tracker devices (e.g. FitBit, Withings) to get access to their genetic report.

Thus, we only considered Impute.me and openSNP for comparison with PAGEANT. Impute.me and openSNP were released in 2015 and in 2011, respectively, supported by companion papers, published in *PLoS One* in 2014 (for openSNP (28)) and in *Frontiers in Genetics* in 2020 (for Impute.me (29)). The main features of Impute.me and openSNP, compared to the ones offered by PAGEANT are reported in Table 2. These two tools provide publicly available source codes and easy-to-access websites. However, they have two main disadvantages: lack of customizability and data confidentiality concerns. Users are not be able to easily customize those tools including the number of traits and the number of SNPs for each trait. In contrast, PAGEANT allows users to customize the genetic report (such as adding/removing traits to be reported, change reference genome to be used) by uploading new files or creating new template-based folders. With regards to data confidentiality, openSNP consists of an open forum for public discussion about the results coming from the interpretation of individual SNPs, previously found to be associated with a certain trait in any of the GWAS carried out so far. The individual genetic data uploaded in openSNP is retained with the aim of providing a public discussion on the obtained results. This may raise important concerns regarding potentially misleading scientific communication within a lay audience.

Impute.me was the most similar resource when comparing it to PAGEANT. Thus, we decided to benchmark PAGEANT exclusively by comparing its performance with Impute.me. Compared to Impute.me, PAGEANT has the advantage of being a standalone tool that could be run on a laptop and without internet connection. In general, a website is more prone to security breach (30). As its name implies, Impute.me actually impute users' genetic data that that process takes up to several days on a personal computer with typical settings. With the sharp decrease of sequencing cost, imputation is likely to become obsolete in the near future. For example, the UK Biobank project is scheduled to conduct whole genome sequencing for all 500 000 participants.

The '5-Q' modules of PAGEANT

The technical implementation of the five-Q modules is shown in Figure 1. PAGEANT is a suite of common bioinformatics software including PLINK (19) to manage and annotate user provided genetic data. The main python script is used to generate the user interface, manage the process and data flow, and eventually generate an easy-to-

Table 2. Comparison of PAGEANT with other 'Academic' DTC genetic testing tools. GDF = genetic data file; NA = not available; PCA = principal component analysis; PRS = polygenic risk score; SNV = single nucleotide variant; UMAP = uniform manifold approximation and projection

	Impute.me	openSNP	PAGEANT
Web-site link	https://www.impute.me/	https://opensnp.org/	https://pageant.me/
Code repository	https://github.com/lassefolkersen/impute-me	https://github.com/gedankenstuecke/snpr	https://github.com/jielab/pageant
Input formats	GDF; VCF	GDF; VCF	GDF; VCF
Retention and sharing	Not retained; user may be contacted for future enrollment in research	Retained; publicly available	Not retained
Imputation	Yes	NO	NO
Genetic ancestry	PCA	NA	PCA/UMAP
Risk/Trait Determination	SNV/PRS	SNV	SNV/PRS
Modules	Complex Diseases; Precision Medicine; UK-BioBank calculator; Appearance; Ethnicity; Drug Response; Rare Diseases; Mutation Senser; BRCA; Politics; Kandinskify yourself; Athletic performance	Genetic prediction based on individual SNV	Complex Diseases; Drug Safety; Main Genetic Characteristics; ClinVar; PharmKGB
Types	Database linking	Database linking	Database linking
Sources	Proprietary reference panel, includes public sources	GWAS Catalog; SNPedia; Mendeley; GET Evidence System; PLoS	Publicly available GWAS summary statistics; customable

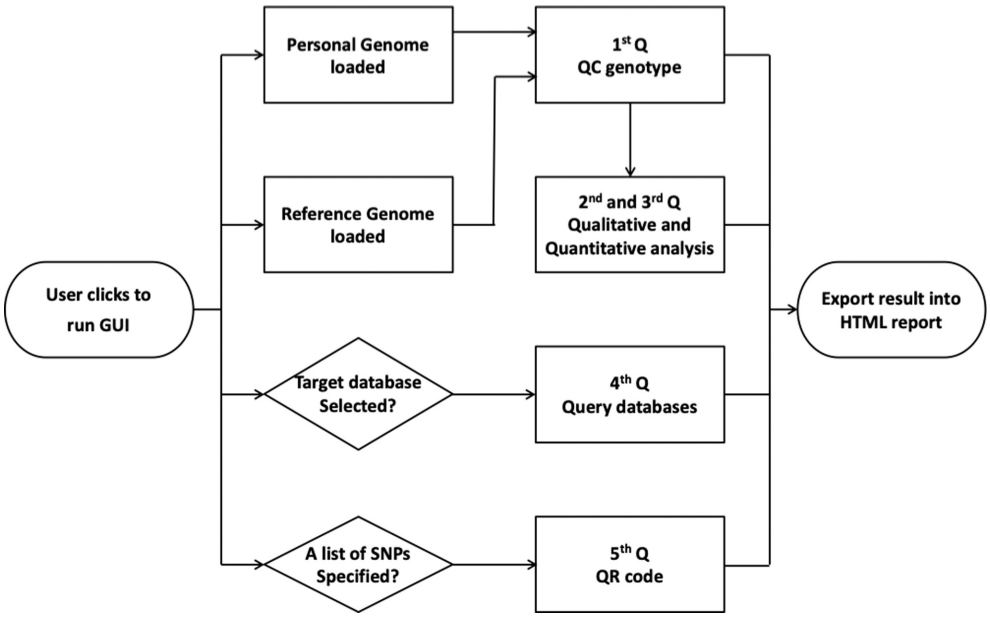


Figure 1. The technical implementation of the five-Q modules.

read report. Figure 2 outlines the file structures when the software is locally installed. Advanced users could work on the folders directly to customize some of the underlying databases and the scope of traits to be reported (Figure 1). The graphical user interface (GUI) was designed in such a way that users could fully customize various parameters before running the full program. It allows users to obtain an example genetic report after loading the GUI interface, by clicking the 'Analyze' button at the bottom of the 'I/O' page (Figure 3A), after selecting the 'Reference population ethnical group' in the 'Quantitative' page (Figure 3B), a necessary step to obtain reliable PRS scores. The GUI page for the five-Q modules is preloaded with default links to key directories and software parameters, which can be customized by advanced users. Advanced users can also customize their genetic report by (i) editing the configuration file; (ii) adding/removing traits to be tested and (iii) replacing PRS reference scoring files in the directory specified in the 'reference population directory' row under the 'Quantitative' menu of the GUI window (Figure 2). The 'reference population ethnical group' dropdown menu on this GUI page will be populated automatically based on the population labels specified in the sample info file.

To enhance the security and the confidentiality of data processing, even if PAGEANT does not store user's data, we implemented three APIs that allow users to access three key components of PAGEANT (Figure 3C). These three APIs could be run standalone, either through the GUI interface or through the command line.

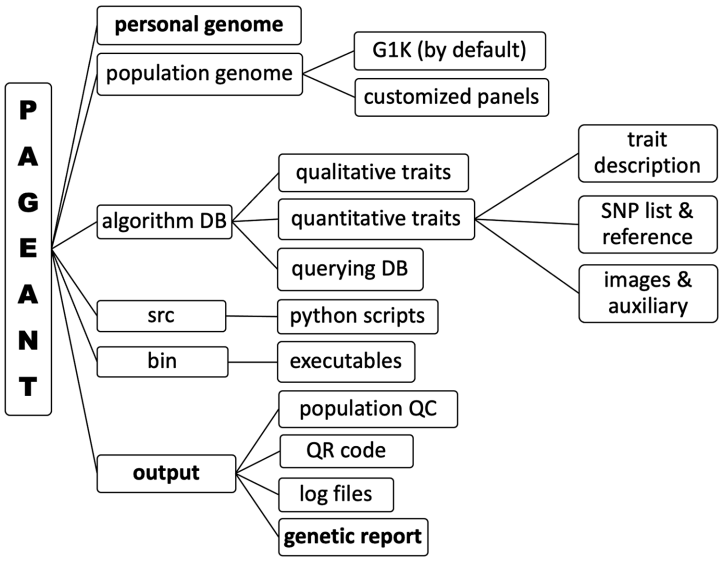


Figure 2. File structures outline when the software is locally installed. Advanced users could also follow this structure to customize the genetic report. For example, under 'algorithm database' folder, there are three files for each trait folder: TRAIT.desc.txt for description text, TRAIT.jpg for a representative picture, TRAIT.snps.ref for a list of SNPs used and the relevant calculation rules. For qualitative traits, the TRAIT.snps.ref has four columns: SNP, genotype, matched, unmatched; For quantitative trait, the TRAIT.snps.ref file requires three columns: SNP, EA (effect allele), BETA or OR (effect size).

First Q: quality assurance and quality control (QA/QC) report of genetic data

By leveraging the PLINK implementation in the PAGEANT software architecture, a basic QC is first performed, including genetically determined sex and the overall missing rate of the user's genotype data, as basic quality assurance. As illustrated in Figure 4, the sample QC report also includes per chromosome distribution of detected variants along with ancestral positioning of personal genome based on PCA and UMAP using the provided population reference (e.g. G1K). A dedicated API is implemented, which could be run easily since the required accessory libraries are already included once PAGEANT is installed (Figure 3C).

Second Q: qualitative assessment for genetic characteristics of absolute or relatively high certainty

This part of the genetic report is intended to present a limited list of genetic characteristics that could be reliably derived and that are of great interest to users. For example, one would want to know his ABO blood type, whether a sprinter or a muscular type person. By default, PAGEANT provides genetic reporting for a list of traits that the authors deemed eligible based on a literature review (Figure 5A). In particular, the list of qualitative traits included by default is based on a simple rule that there is a certain 1–1 relationship between genotype and phenotype. Users have the option to fully customize this list based on their own preference and up-to-update literature. For each listed trait, we recommend that PubMed ID (PMID) be included in the Description section of each trait due to PAGEANT's academic nature.

Third Q: quantitative trait scoring for polygenic traits based on most up to date GWAS literature

When PAGEANT is first launched, the 2504 samples from G1K will have their traits processed first, so that the input individual genomic data has a population reference to measure each trait's relative position among the entire G1K cohort (Figure 5B). One big advantage and innovation of this PAGEANT module is that advanced users could select their preferred GWAS file to calculate PRS. This should be more powerful than those provided by commercial vendors, because their PRS calculation is usually based on a few SNPs and users will not be able to customize it. Raw GWAS files usually come with millions of rows. Besides pruning, the biggest obstacle to adopt a GWAS like this into PAGEANT is that the SNP identifier is different between personal genome and population reference genomes. For example, the reference genome uses rsID as identifier, while many publicly released GWAS files use CHR:POS:REF:ALT format as identifier. Usually this takes an experienced bioinformatician to obtain the SNP identifier format aligned, especially for a GWAS with millions of records. This important function is implemented as an easy-to-use API (Figure 3C).

Fourth Q: query of third party variants databases of interest

As of 29 February 2020, the US National Institutes of Health (NIH) National Center for Biotechnology Information (NCBI) Genetic Testing Registry contained 64 860 genetic tests for 12 268 conditions and 18 686 genes from 560 laboratories (www.ncbi.nlm.nih.gov/gtr). The US Food and Drug Administration (FDA) had 404 entries for pharmacogenomic biomarkers used in drug labeling (www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling) and

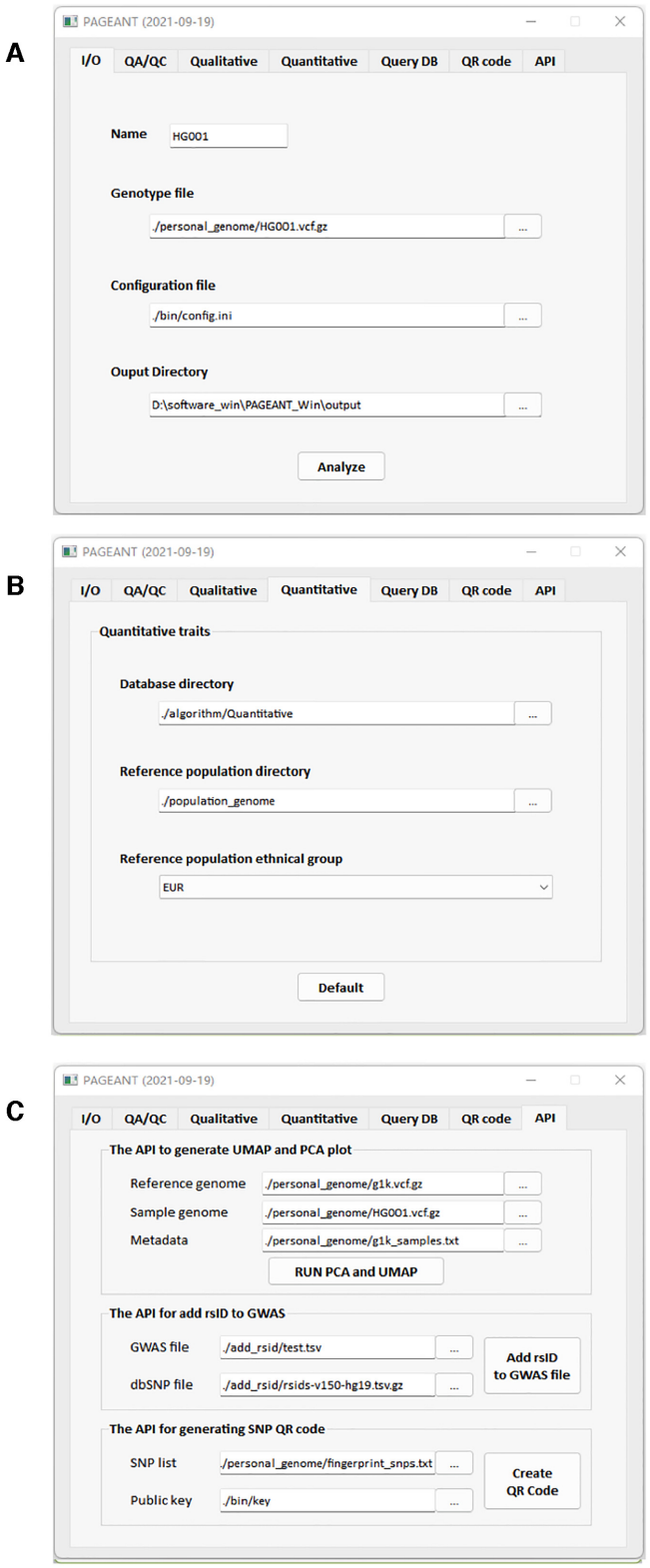


Figure 3. GUI interface of PAGEANT. (**A**) Main page 'I/O'; (**B**) 'Quantitative' page, where the user should select the appropriate ethnical group to obtain reliable PRS; (**C**) 'APIs' page.

published a list of DTC tests with marketing authorization (https://www.fda.gov/medical-devices/vitro-diagnostics/direct-consumer-tests). The default version of PAGEANT allows users to query their genotype data for variants listed in these existing databases thus quickly identify genetic variants of interest (Figure 6).

Fifth Q: quick response (QR) code generation for specified genetic variants

For PAGEANT to extract and transmit a limited amount of genetic data in a convenient approach, we use QR code to code/decode. There are two QR codes involved: the first one is 'public QR code', encoding the list of SNPs (for example, 80 fingerprinting SNPs); the second one is 'private QR code', encoding the actual genomic data of a person for those SNPs coded in the 'public' QR code. To further make this process secure, we implemented the Data Encryption Standard (DES) algorithm for data encryption/decryption on top of coding/decoding. There are two keys involved: the first one is 'public key', which is coded together with the list of SNPs in the public QR code; the second one is 'private key', which is hold only by the person who are authorized to access the limited person genome data. When a user scans the 'public QR code', PAGEANT decodes and decrypts it through DES algorithm, extract the genotype data for the list of SNPs, and then encrypts the extracted genotype data to generate his/her 'private QR code'. This QR code could then be scanned and decrypted only by whoever holds the 'private key'. Figure 7 presents two QR codes for the scenario described above: a 'public QR code' that encodes the 'public key' together with a list of SNPs (on the left), a 'private QR code' that encodes the user's genetic data (on the right). A related API for generating a 'public QR code' that encodes a 'public key' is also available (Figure 3C).

A practical user-case scenario would be the following: (i) A genetic counselor has a list of SNPs that will guide his consultation and prescription. He converted this list of SNPs into a QR code (with 'SNP List' in the center) and put in his clinic. This QR code also embeds a 'public key' to encrypt his SNP list so that it becomes confidential; (ii) a customer scans this QR code and upload it into PAGEANT directory, then PAGEANT extracts his genotype for these SNPs, encrypt the genomic data using the public key, and generates a new QR Code (with the text of 'genome data' in its center); (iii) the genetic counselor scans this customer's QR code, and decrypt the genotype using a private key. Of note, nobody else can decrypt the genotype data without the private key.

DISCUSSION

Currently, DTC genetic testing is typically provided by commercial companies such as Ancestry.com (https://www.ancestry.com/), 23andMe (https://www.23andme.com) and MyHeritage (https://www.myheritage.it/dna). These vendors offer panels which include not only PRS but also carrier status and ancestry records. All these panels are generated starting from DNA taken from a saliva or blood sample then subjected to genotyping on genome-wide chips of up to 1 million variants. Up to the end of 2018, it has been

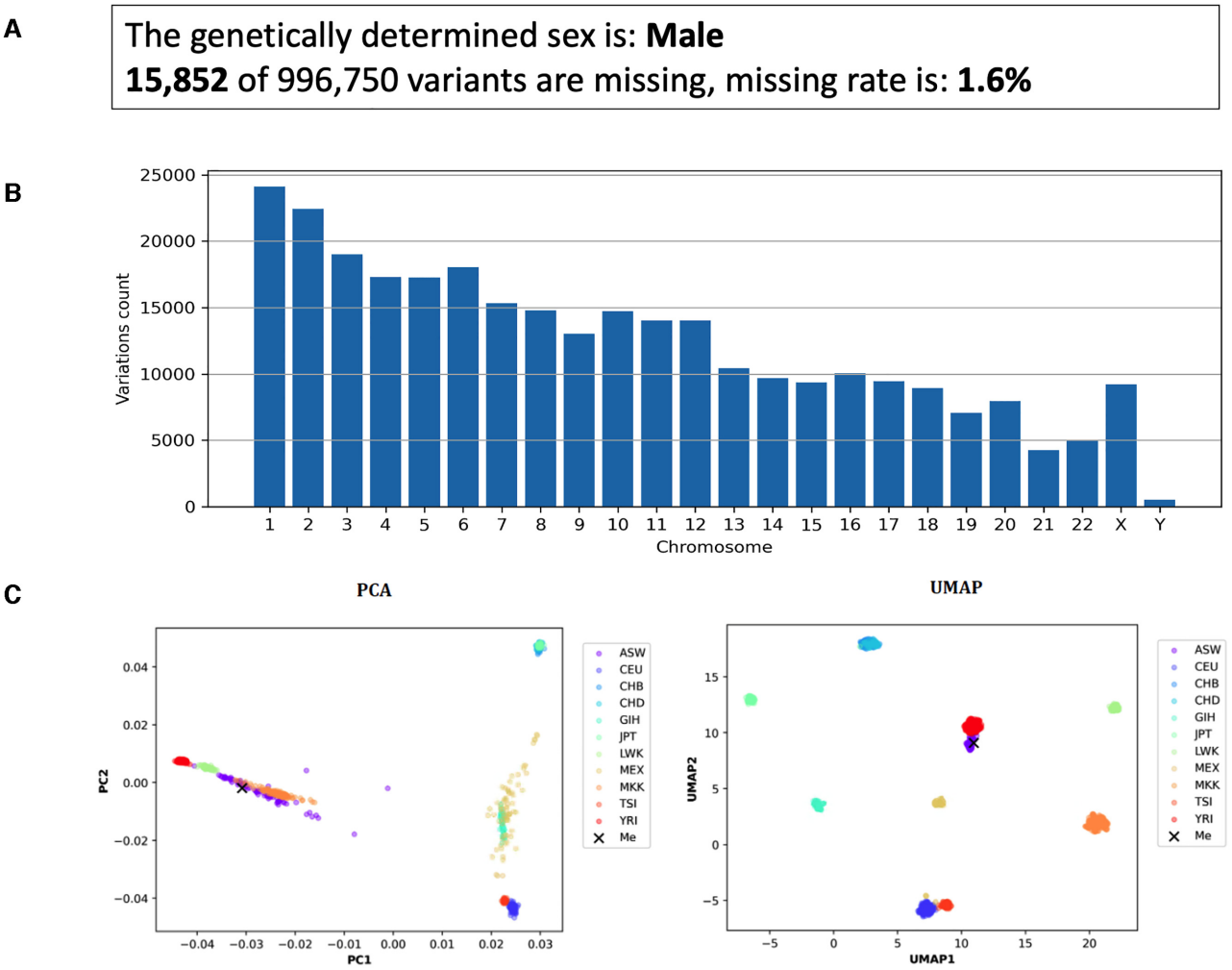


Figure 4. Sample QC report of PAGEANT. (**A**) Genetically determined sex and missingness rate; (**B**) per chromosome count of detected variants; (**C**) ancestral positioning of the personal genome based on principal component analysis {PCA} and uniform manifold approximation and projection {UMAP} using the provided population reference (e.g. G1K). ASW: African Ancestry in Southwest US; CEU: Utah residents (CEPH) with Northern and Western European ancestry; CHB: Han Chinese in Beijing, China; CHD: Chinese in Denver, Colorado; GIH: Gujarati Indian in Houston, TX; JPT: Japanese in Tokyo, Japan; LWK: Luhya in Webuye, Kenya; MEX: Mexican ancestry; MKK: Maasai in Kinyawa, Kenya; TSI: Toscans in Italy; YRI: Yoruba in Ibadan, Nigeria.

estimated that 26 million people had used those online DTC companies (4). Although several consumers are initially interested in ancestry research, they may later opt to use their raw genotype data to explore in third-party interpretation programs to analyze their genetic data for health purposes (31). The information about life itself is undoubtedly much more abundant now and more valuable than 'Google-able' information such as texts and images. However, the interpretation of genetic testing should not mainly rely on those driven by commercial interest and unscientific or inadequate evidences. It is the academic field that is making discovery for genetic mystery of human traits, and we strive to provide an academic version of tool that facilitates the translation of such science into personal access and knowledge. The vision of 6P medicine (participatory, predictive, preventive, personalized, precision, and policy) will forge a big step forward, when the DTC field now focus on getting more and more consumers to participate.

As a proof of concept and demonstration of technological feasibility, we developed PAGEANT (Personal Access to Genome & Analysis of Natural Traits), a DTC and DIY style of genetic reporting tool. PAGEANT is free to use and open for customization. It does not store users' genotype data or mandate the way how the PRS is calculated. Although we provide a default prediction model for a few common traits as a reference by utilizing published results from GWAS Catalog, we also allow users to customize or even completely design their own model.

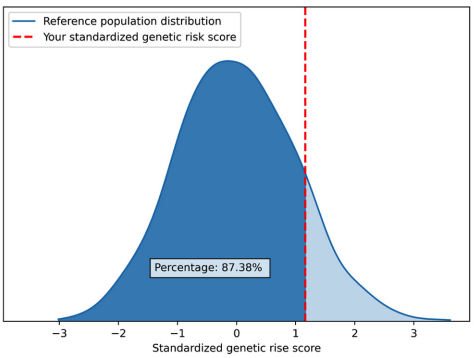
We also explored how to utilize the widely adopted QR code to securely transmit a small amount of personal genetic data. Previously, researchers developed Medicine Safety Code service to enable physicians and patients to represent pharmacogenomic data in QR code at the point-of-care (32). The approach implemented in PAGEANT differs for two aspects: (i) PAGEANT allows extracting genotype in real-time, based on physician' list of SNPs;

A

Qualitative Traits	Result
ABO blood type	B
Alcohol flush	A-
APOE type	ε3/ε3
Folic Acid metabolism	Slow
FTO rs9939609	Wild type
HIV resistance	Wild type
Lactose metabolism	Lactose tolerance
Muscle fiber type	Fast muscle type
Nicotine addiction	Wild type
Altruism	More likely
Earwax Type	Wet
Perception of fish odor	Insensitive
Caffeine metabolism	Slow
Marital satisfaction	Normal

B

Quantitative Traits	Result
Age related macular degeneration	Normal
Colorectal cancer	Low risk
Atrial fibrillation	Low risk
Coronary artery disease	Normal
Lung cancer	High risk
Migraine	Low risk
Schizophrenia	High risk
Breast Cancer	Low Risk
COVID-19 susceptibility	Low risk
COVID-19 critical illness	Normal



Standardized PR: Mean + 1.16 * SD
Distribution:
- ❑ **N of reference population:** 2504
- ❑ **N below this sample:** 2188 (87.38%)
- ❑ **N above this sample:** 316 (12.62%)

Figure 5. Qualitative and quantitative trait report output. PAGEANT provides (**A**) genetic reporting for a list of qualitative traits that the authors deemed eligible based on a literature review and (**B**) quantitative trait scoring for polygenic traits based on most up to date GWAS literature.

Clinvar

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Variant	Allele	Allele type	Genotype	Clinvar ID
rs716274	G	Drug response	GG	226013
rs9332131	G	Drug response	GAGA	285601
rs10066882	A	Conflicting interpretations of pathogenicity	CC	414373
rs1041983	T	Drug response	CC	375653
rs10979599	T	Conflicting interpretations of pathogenicity	GG	245634
rs11078699	T	Conflicting interpretations of pathogenicity	CC	387361
rs11104729	C	Conflicting interpretations of pathogenicity	TT	261849
rs11466016	A	Conflicting interpretations of pathogenicity	CC	36516
rs11541998	T	Conflicting interpretations of pathogenicity	CC	732303
rs11549709	A	Conflicting interpretations of pathogenicity	GG	136294

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Figure 6. Query of third party variants databases of interest (PharmKB, ClinVAR).

(ii) PAGEANT implements encryption/decryption besides coding/decoding, which is important for private patient genetic data. A patient has full control over all his/her private genomic data, only giving necessary genotype to the physician. And the physician also has full control on the medical interpretation of genetics. For example, if the patient has a pathogenic mutation for cancer, the physician may decide to not show it to the patient. As already stated in the introduction, it is not within the aims of the present paper to discuss about the pros and cons of DTC genetic testing or the ethical implications when getting genetically tested. A quite large literature is available on this matter (14–18,26,30).

Overall, PAGEANT represents a new, publicly available tool for third party genetic interpretation, that is totally transparent in its functionalities, so that the source code

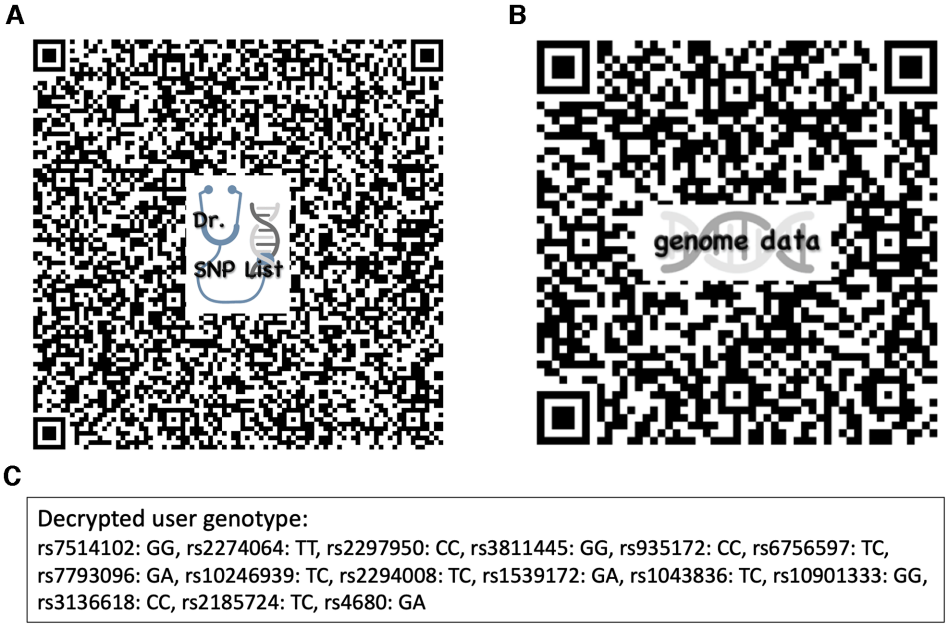

Figure 7. Quick response (QR) code generation for specified genetic variants. (**A**) QR code for public key and SNP list; (**B**) QR code for user's genotype data; (**C**) decrypted user genotype.

provided can be used for direct customization by the user and to expand the general knowledge about the 'secrets' behind DTC genetic testing results interpretation. The output genetic report enabled displaying the log information of running the program so that users can quickly make sense of the underlying process and spot potential bugs. We want to highlight the great potential of PAGEANT also in the didactive context, by helping in training, preparing, and informing the next generation of scientists and clinically trained professionals that will face the ongoing race in personalized medicine businesses.

DATA AVAILABILITY

PAGEANT code is available at https://github.com/jielab/pageant.

SUPPLEMENTARY DATA

Supplementary Data are available at NAR Online.

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Conflict of interest statement. None declared.

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