ARTICLE

Robust Replication of Genotype-Phenotype Associations across Multiple Diseases in an Electronic Medical Record

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Large-scale DNA databanks linked to electronic medical record (EMR) systems have been proposed as an approach for rapidly generating large, diverse cohorts for discovery and replication of genotype-phenotype associations. However, the extent to which such resources are capable of delivering on this promise is unknown. We studied whether an EMR-linked DNA biorepository can be used to detect known genotype-phenotype associations for five diseases. Twenty-one SNPs previously implicated as common variants predisposing to atrial fibrillation, Crohn disease, multiple sclerosis, rheumatoid arthritis, or type 2 diabetes were successfully genotyped in 9483 samples accrued over 4 mo into BioVU, the Vanderbilt University Medical Center DNA biobank. Previously reported odds ratios (OR_{PR}) ranged from 1.14 to 2.36. For each phenotype, natural language processing techniques and billing-code queries were used to identify cases ($n = 70$–698) and controls ($n = 808$–3818) from deidentified health records. Each of the 21 tests of association yielded point estimates in the expected direction. Previous genotype-phenotype associations were replicated ($p < 0.05$) in 8/14 cases when the OR_{PR} was > 1.25, and in 0/7 with lower OR_{PR}. Statistically significant associations were detected in all analyses that were adequately powered. In each of the five diseases studied, at least one previously reported association was replicated. These data demonstrate that phenotypes representing clinical diagnoses can be extracted from EMR systems, and they support the use of DNA resources coupled to EMR systems as tools for rapid generation of large data sets required for replication of associations found in research cohorts and for discovery in genome science.

Introduction

The deployment of electronic medical record (EMR) systems offers the hope of improving routine care, not only by enhancing individual practitioner access to patient information but also by aggregating information for clinical research and quality improvement.[1] EMRs and associated support systems can reduce medication errors, costs, and inappropriate testing and improve quality of care, physician documentation, and guideline adherence.[2–8]

Because EMRs contain large populations with diverse diseases, they have the potential to act as platforms for generating sets of cases and controls for clinical and translational research. Potential advantages of such an approach include rapid and inexpensive creation of large, inclusive patient sets,[9] as well as support for studies of disease-disease or disease-drug interactions over time. An especially appealing, albeit complex, vision is one in which dense genomic information is accrued into EMRs, ultimately enabling discovery and incorporation into practice of new genotype-phenotype associations.[10–12]

Implementing such a vision requires that major obstacles be overcome, including technological, computational, ethical, and financial issues, and determining whether genomic information will meaningfully inform clinical decision making and healthcare outcomes. An important hypothesis to be tested[13] is the idea that large biorepositories containing DNA samples linked to EMRs can be used to address these challenges to augment or supplement traditional research designs in which cases and controls are prospectively enrolled and phenotype data are systematically collected.

BioVU, the Vanderbilt DNA databank,[14] represents such a biorepository. To test the utility of the resource in addressing these challenges, we genotyped the first ~10,000 samples accrued (over 4 mo) for SNP sites reproducibly associated with a range of human diseases. Automated queries were then developed, validated, and deployed for the identification of cases and controls in five common diseases, and previously reported genotype-phenotype relationships were examined. Our results provide support for the concept that biorepositories linked to "real-world" EMR data represent robust tools for accelerating genome-driven diagnostics and therapeutics.

Subjects and Methods

Inclusion and Exclusion Criteria

BioVU accrues DNA samples extracted from blood remaining from routine clinical testing after the samples have been retained for 3 days and are scheduled to be discarded. A full description of the resource and its ethical protections has been published elsewhere.[14] The resource contains data and tissues that are deidentified in accordance with provisions of Title 45, Code of Federal Regulations, part 46 (45 CFR 46) that define criteria for

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investigations that are considered "nonhuman subjects" research. Exclusion criteria are as follows: poor-quality or insufficient DNA, age < 18 yrs, absence of a signed consent-to-treatment form, a formal indication (on the consent-to-treatment form or elsewhere) that an individual wishes to opt out, or duplicate samples. In addition, a small percentage (~2%) of patients is randomly excluded from BioVU so that it is not possible to know whether any individual's sample is or is not included in the biobank. The project has been reviewed and approved at multiple levels, including the institutional review board, internal and external ethics committees, the community advisory board and the legal department (Nashville, TN, USA), as well as the Federal Office of Human Research Protection (Washington, D.C., USA), and this oversight is ongoing. As of March 22, 2010. the resource included 80,635 samples, with an accrual rate of ~500–700 per wk.

Phenotypes and Genotypes Analyzed

Our aim was to study SNPs previously and reproducibly associated in GWAS with susceptibility to common diseases and to determine whether those associations could be replicated with the use of only the information derived from the EMR to determine case and control status. The conditions chosen were atrial fibrillation (AF),[15] Crohn disease (CD),[16–18] multiple sclerosis (MS [MIM 126200]),[19,20] rheumatoid arthritis (RA [MIM 180300]),[16,21] and type 2 diabetes (T2D [MIM 125853]), because there were several single locus hits to replicate for each disorder and the diseases varied in level of difficulty for the EMR phenotype abstraction.[16,22–24] The assayed SNPs and their primer sequences are presented in Table S1, available online. We selected 21 SNPs that had consistently shown replication for these diseases by late 2007; SNP associations studied after this date were therefore not included. The individuals studied were accrued in the first 4 mo of operation of the resource.

We selected this set of diseases and SNPs to ask the question of whether EMR-derived phenotypes can be used for human genetic-association studies. The previously reported odds ratios (OR_{PR}) for the SNPs that we examined ranged from 1.14 to 2.36. Table S1 also presents power calculations[25] performed in determining the sample size needed to replicate each OR_{PR} at 80% power, given reported allele frequencies in cases and controls for each disease, for determining whether we were powered to detect the selected effects.

Identifying Cases and Controls

For each disease, cases and controls were identified in the Synthetic Derivative, a deidentified image of the EMR linked to BioVU by anonymous research unique identifiers.[14] The Vanderbilt EMR began accumulating clinical data in the early 1990s and now includes all inpatient and outpatient billing codes, laboratory values, reports, and clinical documentation, almost all in electronic formats available for searching. It currently contains over 120 million documents on about 2 million patients.[26] The synthetic derivative is refreshed monthly to add new clinical information from the EMR as it is accrued.

For each disease, content experts (listed in Acknowledgments) were consulted to develop algorithms that segmented the deidentified EMR data into four groups: definite cases (algorithm-defined); possible cases (requiring manual curation); exclusions for matching potentially overlapping diseases or symptoms or insufficient data for classifying; and controls (algorithm-defined). The selection algorithms are presented in the Appendix. In brief, cases were selected via disease-specific combinations of billing codes, patient encounters, laboratory data, and natural language processing (NLP) techniques on unstructured patient records such as medications, electrocardiograms, or past medical history. To define controls, we adopted criteria to ensure that the diagnosis had been sought and was absent. This generally included visits to primary care or internal medicine clinics with nonempty "past medical history" sections and medication lists. In addition, controls for atrial fibrillation all had electrocardiograms that did not show atrial fibrillation. We also excluded potentially overlapping conditions, such as other inflammatory arthritides from rheumatoid arthritis controls and autoimmune diseases from rheumatoid arthritis, multiple sclerosis, and Crohn disease controls.

Initial algorithms were developed to identify records from each of the four classifications from the samples in the synthetic derivative, and the results were reviewed by two physicians not associated with algorithm development. The results of the manual classification were then used to improve the algorithms, and the procedure was iterated until the positive predictive value (PPV) reached designated targets of ≥ 95% for definite cases and ≥ 98% for controls. In each algorithm iteration, the physicians reviewed a different set of 50 randomly selected cases and controls, and the final algorithm-performance numbers represent the performance of the algorithm on a test set not previously reviewed by either the algorithm developers or the physician reviewers. The final algorithms were then applied to the initial BioVU sample set of 9483 subjects. Populations for cases and controls for rheumatoid arthritis, Crohn disease, atrial fibrillation, and type 2 diabetes were defined exclusively by the final algorithm. Each phenotype algorithm was run on the full set of 9483 subjects such that a particular person could be a case for one condition, a control for one or more other conditions, or unknown for one or more other conditions. Because of the low count of definite and possible cases for multiple sclerosis, we tuned the multiple sclerosis algorithm for sensitivity and the physician reviewers manually reviewed the electronic records of all definite and possible cases.

Data Analysis

Genotyping was conducted by the Vanderbilt DNA Resources Core with the use of the midthroughput Sequenom genotyping platform, based on a single-base primer extension reaction coupled with mass spectrometry. Quality-control procedures included examination of marker and sample genotyping efficiency, allele-frequency calculations, and tests of Hardy-Weinberg equilibrium (HWE). As described in Results, some SNPs poorly assayed on the Sequenom platform (as indicated by deviations from HWE) were regenotyped with TaqMan assays and the ABI Prism 7900HT Sequence Detection System (Applied Biosystems).

Ancestry was derived from administrative data recorded in the EMR; 9.2% of records did not include recorded ancestry or recorded the ancestry as "unknown." Accordingly, the data were analyzed with respect to ancestry in two different ways. In the first, only cases and controls that had "non-Hispanic white" (European American) coded in the EMR were used, whereas in the second, records designated as either "non-Hispanic white" or "unknown" were included. Preliminary data directly examining ancestry-informative markers in the BioVU "unknown" group indicate that > 85% of cases cluster with European Americans (Ritchie et al., poster presented as part of the Illumina Technology Workshops at the ASHG 59th Annual Meeting, Honolulu, HI, USA, October 22, 2009). Thus, we expect that both the non-Hispanic white and the non-Hispanic white + unknown records are primarily European American.

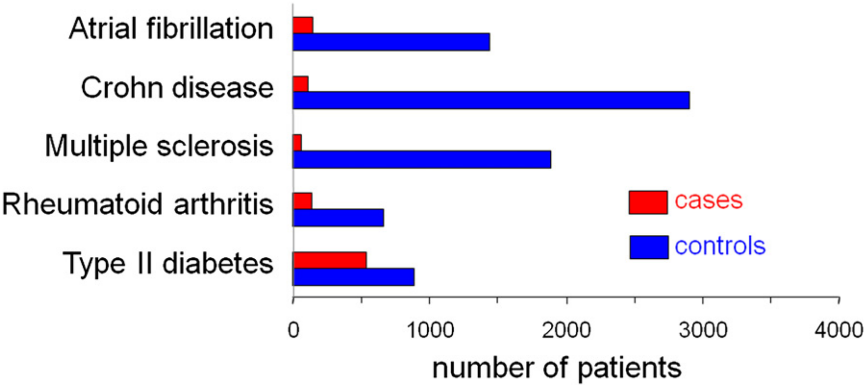


Figure 1. Identifying Cases and Controls
The numbers presented are for European American subjects, with a definite diagnosis. Table S2 presents the numbers for other groupings studied here.

Single-locus tests of association (cases versus controls) were conducted for each previously reported SNP. We calculated allelic (chi-square) and genotypic (logistic regression) ORs and 95% confidence intervals (CIs) for dominant, additive, and recessive genetic models. All statistical analyses were conducted in SAS, version 9.1, with the use of two-tailed tests.

Role of the Funding Source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Identifying Cases and Controls

The positive predictive values of case and control selection algorithms were 97%–100%, except for multiple sclerosis, in which algorithm-classified possible cases were also manually reviewed because of small sample size (Table S2). For the rheumatoid arthritis and multiple sclerosis phenotypes, we identified both definite cases and definite cases with other, potentially overlapping, autoimmune diseases ("probable cases"): for rheumatoid arthritis, there were 174 definite cases of European ancestry and 346 definite + probable cases of European or unknown ancestry, and the corresponding figures for multiple sclerosis were 70 and 124, respectively.

Figure 1 shows the distribution of cases and controls across the five phenotypes analyzed. In the set of 9483 records analyzed by NLP for the five diseases, there were 1212 definite cases of European ancestry and 5114 controls. There were 4072 that served as either a case or a control in more than one analysis.

Genotyping

A total of 9483 samples were genotyped for 23 SNPs across the five diseases with the use of the Sequenom platform. We excluded 1847 samples with genotyping efficiency < 90% from data analysis. These failures were primarily from the first several plates processed and reflected the fact that this was the first set of DNA samples genotyped with the use of the Sequenom technology in the DNA Resources Core facility. Genotyping efficiency for individual SNPs varied from 95.4%–100% (Table S3). The number of definite cases of European ancestry in which genotyping was successful ranged from 61 (multiple sclerosis) to 510–533 (type 2 diabetes; depending on the specific SNP), with 658–2884 controls (Table 1 and Table S4).

Four SNPs were flagged because of significant deviations from HWE at $p < 0.05$. Two of these (rs7901695 and rs7903146), both in *TCF7L2* (MIM 602228) and associated with type 2 diabetes, are in linkage disequilibrium with other markers studied here in the same gene (based on the HapMap) and so were eliminated from further analysis. One rheumatoid arthritis-associated SNP in the *HLA* cluster on chromosome 6 (MIM 142860), rs6457617, could not be successfully assayed with Sequenom or TaqMan. We therefore dropped this SNP and instead genotyped rs6457620 by using a TaqMan assay (genotyping efficiency = 99.46%; HWE p value = 0.26). The SNP rs6457620 is in complete linkage disequilibrium with rs6457617 ($r^2 = 1$) in the International HapMap Project samples of European ancestry (CEU).[27] The fourth SNP, rs2200733, an atrial-fibrillation-associated variant, had low genotyping efficiency in addition to deviation from HWE ($p < 0.05$). This SNP was successfully genotyped with TaqMan (genotyping efficiency = 99%; HWE p value = 0.64). The final analysis therefore included 21 SNPs.

Genotype-Phenotype Associations

The number of cases needed to achieve 80% power at $\alpha = 0.05$ for the SNPs studied varied widely, from 75 to 3111, assuming a 1:2 ratio of cases versus controls (Table S1). This range reflects the OR_{PR} and minor allele frequencies (MAFs) in cases and controls. Table S1 also presents the number of cases needed assuming other ratios of cases to controls, from 1:1 to 1:4. Increasing the number of controls 4-fold resulted in a modest reduction, ~30%, of the cases needed.

Figure 2 presents the calculated allelic OR and 95% CIs, with the use of definite cases and controls and European ancestry only. In addition to the results from BioVU data, we plot the OR for the original GWAS result; subsequent publications confirming these results have very similar values (data not shown). For example, the SNP rs4506565 in *TCF7L2* has previously been associated with type 2 diabetes, with an OR_{PR} of 1.37 and MAFs of 0.32 in cases and 0.39 in controls.[24] To replicate this finding assuming a similar genetic effect size, we would need to identify 503 cases and 1006 controls. Genotyping in subjects identified by the phenotype algorithms resulted in 532 definite cases (MAF 0.35) and 886 controls (MAF 0.31), resulting in a calculated allelic OR of 1.29 (95% CI: 1.09–1.53; $p = 0.009$; Table S4). The genotypic OR was 1.23 (1.05–1.45; $p = 0.006$; Table S4). Homozygotes for the minor (risk) allele had an OR of 1.7 (1.22–2.38; $p = 0.0016$) compared to homozygotes for the major allele or heterozygotes. The results were very similar when the 553 cases and 1100 controls of European or unknown ancestry were analyzed. Table 1 presents the results of all allelic analyses, and Table S4 presents the genotypic analyses, for both European and European + unknown ancestry, and for definite as well as definite + probable cases (rheumatoid arthritis and multiple sclerosis).

All 21 comparisons resulted in OR point estimates in the expected direction, and for each of the five diseases studied, at least one previously reported SNP association was replicated ($p < 0.05$ for allelic OR). Two sets of SNPs in type 2 diabetes were in LD with one another and, comfortingly, showed similar results. The SNPs rs4506565, rs1224332, and rs225537 (in or near *TCF7L2*) have pairwise r^2 values of between 0.658 and 0.902; all three SNPs were statistically significantly associated with type 2 diabetes. Similarly, rs5215 and rs5219 (in *KCNJ11* [MIM 600937]) have a pairwise r^2 of 0.994, and both were nonsignificant. The analyses in Figure 2 are ordered by the number of cases required for replication, and they show that the fewer cases required, the greater the likelihood of replication with 95% CIs of the point estimate not overlapping unity. When fewer than 1000 cases were required, 8/12 associations replicated in this fashion, whereas there was no replication (0/9) of associations predicted to require more than 1000 cases. Similarly, a low OR_{PR} implied that a large number of cases would be required for replication: indeed, 8/14 associations with an $OR_{PR} > 1.25$ replicated, in contrast to 0/7 with $OR_{PR} \leq 1.2$.

Analyses that included the slightly larger numbers of subjects whose ancestry was European or unknown yielded the same results: replication of the same 8/14 associations with $OR_{PR} > 1.25$. When both definite and probable cases for rheumatoid arthritis and multiple sclerosis were included in the case series, one more association was replicated in the rheumatoid arthritis set (Table 1).

Discussion

We demonstrate here that common genetic variants associated with disease can be replicated with the use of samples from a DNA databank coupled to a deidentified EMR, in effect rejecting the null hypothesis that EMR-derived phenotypes are insufficiently distinct or detailed to identify such associations that historically have been observed in carefully characterized research cohorts. We examined SNPs with a wide range of OR_{PR}, from 1.14 to 2.36, and showed that the likelihood that we could replicate any genotype-phenotype association in this set of 9483 records varied directly with the genetic effect size of the previously reported association. These records were selected because they were the first accrued into the resource and were accrued with no knowledge of underlying disease frequencies. The time required to generate this set from which the cases and controls were identified was only 4 mo.

Accruing, defining, and accessing samples presented multiple technical challenges, so establishing appropriate quality-control checks was vital to the success of this experiment and to use of any biorepository. Before genotyping and phenotyping, we validated sample-handling algorithms by using gender testing, as previously reported.[14] A critical challenge was the definition of cases and controls, both of which represent unique challenges in the EMR and require nuanced application of information-extraction techniques. It was not unusual to find cases in which a rheumatoid arthritis or multiple sclerosis code from the International Statistical Classification of Diseases and Related Health Problems, revision 9 (ICD-9 code) was associated with a clinic visit, only to have the diagnosis subsequently overturned by a specialist consultation. Thus, the case definitions each relied on both coded and unstructured, free-text data, such as diagnoses, medications, or laboratory findings. Similarly, the criteria for controls were not simply the absence of the condition, but also included the absence of clinically similar conditions and included documentation that the condition was sought as well as absence of clinically similar conditions. Assurance that controls do not have the disease is especially important for relatively common diseases such as diabetes, although it is potentially less impactful for rare diseases such as multiple sclerosis. To avoid introduction of bias in our control populations by overly restrictive criteria, these algorithms ensured that control subjects did not have the case (or similar) diseases through clinic visits with past medical history assessments, common laboratory values, and normal electrocardiograms.

The BioVU DNA Databank currently uses ancestry assigned in administrative (e.g., billing) databases. The 9483 records analyzed included 77% European American, 11% African American, 1% Hispanic, 1% Asian, and 1% other; an explicit statement of ancestry is absent in 9% of records. Including the samples of unknown ancestry did not alter the results, possibly because the majority of our population is non-Hispanic European American. The accuracy of ancestry information contained in administrative databases is unknown, although self-reported ancestry agrees well with genetically determined race.[28] Our current evaluation of the ancestry of the "unknown" population of BioVU indicates that the majority of these individuals are European American (Ritchie et al., poster presented as part of the Illumina Technology Workshops at the ASHG 59th Annual Meeting, Honolulu, HI, USA, October 22, 2009).

Although EMR-based phenotyping can be complex, as discussed above, the approach also has potential

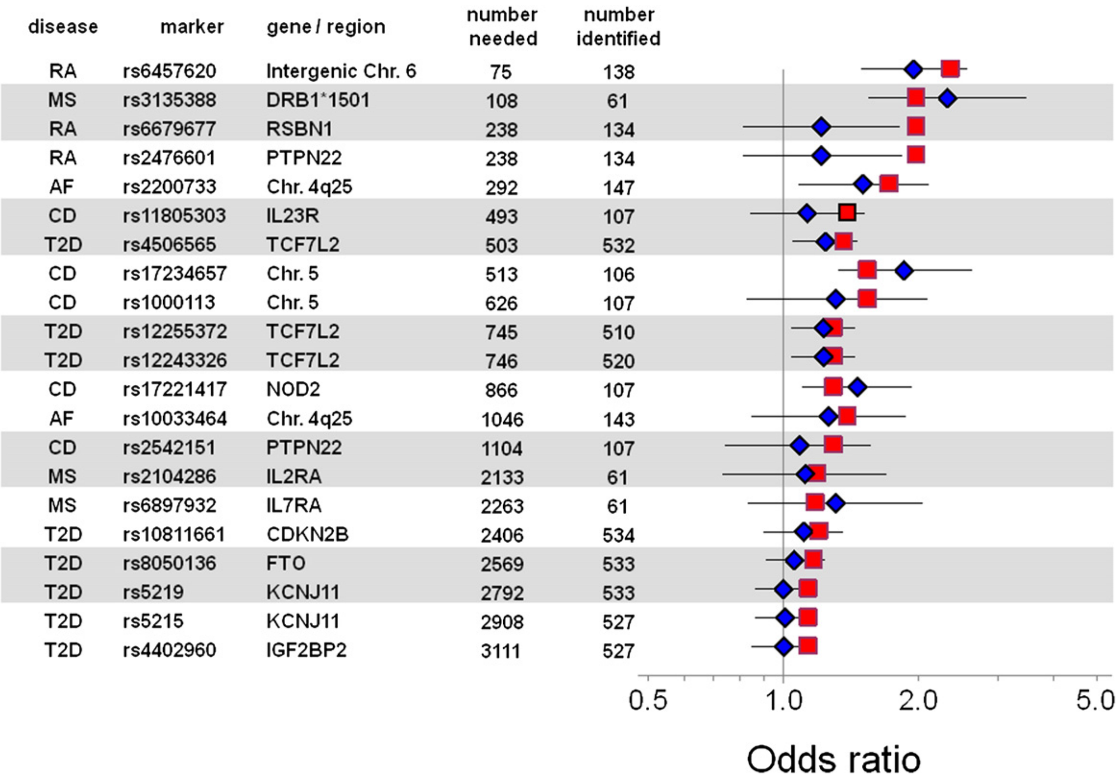
Table 1. Allelic Odds Ratio

	Cases	Controls	Cases	Cases	Controls	Controls			
SNP	**N**	**N**	**Minor Allele Frequency**	**Minor Allele**	**Minor Allele Frequency**	**Minor Allele**	**Allelic Chi-Square p Value**	**Odds Ratio**	**95% Confidence Interval**
ATRIAL FIBRILLATION									
Ancestry: Non-Hispanic European; Case Definition: Definite									
rs2200733	147	1439	0.1599	T	0.1120	T	0.0147	1.5093	(1.08–2.11)
rs10033464	143	1402	0.1084	T	0.0881	T	0.2530	1.2585	(0.85–1.87)
Ancestry: Non-Hispanic European + Unknown; Case Definition: Definite									
rs2200733	148	1467	0.1588	T	0.1115	T	0.0153	1.5048	(1.08–2.10)
rs10033464	144	1432	0.1111	T	0.0887	T	0.2066	1.2844	(0.87–1.90)
CROHN DISEASE									
Ancestry: Non-Hispanic European; Case Definition: Definite									
rs11805303	107	2884	0.3271	T	0.3017	T	0.4263	1.1253	(0.84–1.51)
rs17234657	106	2890	0.2028	G	0.1201	G	0.0003	1.8646	(1.32–2.63)
rs1000113	107	2905	0.0935	T	0.0730	T	0.2601	1.3096	(0.82–2.10)
rs17221417	107	2896	0.3785	G	0.2949	G	0.0086	1.4562	(1.10–1.93)
rs2542151	107	2901	0.1542	G	0.1649	G	0.6774	1.0834	(0.74–1.58)
Ancestry: Non-Hispanic European + Unknown; Case Definition: Definite									
rs11805303	110	3175	0.3288	T	0.3054	T	0.4557	1.1145	(0.84–1.45)
rs17234657	110	3182	0.1955	G	0.1204	G	0.0009	1.7756	(1.23–2.50)
rs1000113	111	3199	0.0946	T	0.0769	T	0.3323	1.2542	(0.79–1.98)
rs17221417	111	3188	0.3874	G	0.2917	G	0.0021	1.5353	(1.17–2.02)
rs2542151	111	3195	0.1577	G	0.1635	G	0.8158	1.0446	(0.72–1.51)
MULTIPLE SCLEROSIS									
Ancestry: Non-Hispanic European; Case Definition: Definite									
rs6897932	61	1861	0.2049	T	0.2515	T	0.2425	1.3036	(0.83–2.04)
rs3135388	61	1892	0.2887	T	0.1427	T	<0.0001	2.3210	(1.55–3.48)
rs2104286	61	1888	0.2377	A	0.2582	A	0.6102	1.1163	(0.73–1.70)
Ancestry: Non-Hispanic European + Unknown; Case Definition: Definite									
rs6897932	88	2105	0.2045	T	0.2485	T	0.1855	1.2857	(0.89–1.87)
rs3135388	88	2139	0.2955	T	0.1431	T	<0.0001	2.5120	(1.80–3.51)
rs2104286	88	2133	0.2102	A	0.2586	A	0.1503	1.3101	(0.91–1.89)
Ancestry: Non-Hispanic European; Case Definition: Definite + Probable									
rs6897932	68	1861	0.2132	T	0.2515	T	0.3118	1.2396	(0.82–1.88)
rs3135388	68	1892	0.2574	T	0.1427	T	0.0002	2.0818	(1.40–3.09)
rs2104286	68	1888	0.2279	A	0.2582	A	0.4275	1.1790	(0.78–1.77)
Ancestry: Non-Hispanic European + Unknown; Case Definition: Definite + Probable									
rs6897932	96	2105	0.2083	T	0.2485	T	0.2072	1.2563	(0.88–1.79)
rs3135388	96	2139	0.2760	T	0.1431	T	<0.0001	2.2840	(1.65–3.17)
rs2104286	96	2133	0.2083	A	0.2586	A	0.1190	1.3252	(0.93–1.89)

Table 1. ***Continued***

	Cases	Controls	Cases	Cases	Controls	Controls			
SNP	**N**	**N**	**Minor Allele Frequency**	**Minor Allele**	**Minor Allele Frequency**	**Minor Allele**	**Allelic Chi-Square p Value**	**Odds Ratio**	**95% Confidence Interval**
RHEUMATOID ARTHRITIS									
Ancestry: Non-Hispanic European; Case Definition: Definite									
rs6679677	134	658	0.1194	A	0.1003	A	0.3496	1.2162	(0.81–1.83)
rs2476601	134	659	0.1194	A	0.1002	A	0.3454	1.2183	(0.81–1.84)
rs6457620	138	662	0.3370	T	0.4977	T	<0.0001	1.9501	(1.49–2.56)
Ancestry: Non-Hispanic European + Unknown; Case Definition: Definite									
rs6679677	184	745	0.1141	A	0.0943	A	0.2609	1.2326	(0.86–1.78)
rs2476601	184	746	0.1141	A	0.0945	A	0.2576	1.2344	(0.86–1.88)
rs6457620	188	750	0.3601	T	0.4973	T	<0.0001	1.6689	(1.33–2.09)
Ancestry: Non-Hispanic European; Case Definition: Definite + Probable									
rs6679677	210	658	0.1286	A	0.1003	A	0.1029	1.3235	(0.94–1.85)
rs2476601	210	659	0.1262	A	0.1002	A	0.1319	1.2975	(0.92–1.82)
rs6457620	214	662	0.3626	T	0.4977	T	<0.0001	1.7422	(1.39–2.18)
Ancestry: Non-Hispanic European + Unknown; Case Definition: Definite + Probable									
rs6679677	272	745	0.1250	A	0.0946	A	0.0459	1.3667	(1.00–1.86)
rs2476601	272	746	0.1232	A	0.0945	A	0.0589	1.3459	(0.99–1.83)
rs6457620	277	750	0.3776	T	0.4896	T	<0.0001	1.6521	(1.35–2.02)
TYPE 2 DIABETES									
Ancestry: Non-Hispanic European; Case Definition: Definite									
rs4402960	527	877	0.3083	T	0.3079	T	0.9787	1.0023	(0.85–1.18)
rs10811661	534	887	0.1610	C	0.1753	C	0.3269	1.1074	(0.90–1.36)
rs4506565	532	886	0.3524	T	0.3053	T	0.0093	1.2384	(1.05–1.46)
rs12243326	520	876	0.3212	C	0.2785	C	0.0169	1.2253	(1.04–1.45)
rs12255372	510	847	0.3245	T	0.2816	T	0.0178	1.2257	(1.04–1.45)
rs5215	527	882	0.3672	C	0.3702	C	0.8728	1.0130	(0.86–1.19)
rs5219	533	888	0.3715	T	0.3705	T	0.9580	1.0042	(0.86–1.18)
rs8050136	533	886	0.4053	A	0.3916	A	0.4731	1.0584	(0.91–1.24)
Ancestry: Non-Hispanic European + Unknown; Case Definition: Definite									
rs4402960	548	1089	0.3139	T	0.3159	T	0.9067	1.0094	(0.86–1.18)
rs10811661	555	1103	0.1604	C	0.1727	C	0.3700	1.0931	(0.90–1.33)
rs4506565	553	1100	0.3535	T	0.3100	T	0.0117	1.2172	(1.04–1.42)
rs12243326	541	1088	0.3226	C	0.2845	C	0.0251	1.1976	(1.02–1.40)
rs12255372	530	1048	0.3236	T	0.2863	T	0.0305	1.1928	(1.02–1.40)
rs5215	547	1098	0.3656	C	0.3643	C	0.9404	1.0057	(0.87–1.17)
rs5219	554	1103	0.3700	T	0.3649	T	0.7728	1.0223	(0.88–1.19)
rs8050136	554	1102	0.4043	A	0.3897	A	0.4177	1.0628	(0.92–1.23)

advantages. In some instances, the case diagnosis can be firmer than that in prospective clinical trials or case-control studies, because longitudinal information from multiple, interacting, trained physicians is available. For example, differentiating Crohn disease from other conditions such as ulcerative colitis benefits from longitudinal



disease	marker	gene / region	number needed	number identified
RA	rs6457620	Intergenic Chr. 6	75	138
MS	rs3135388	DRB1*1501	108	61
RA	rs6679677	RSBN1	238	134
RA	rs2476601	PTPN22	238	134
AF	rs2200733	Chr. 4q25	292	147
CD	rs11805303	IL23R	493	107
T2D	rs4506565	TCF7L2	503	532
CD	rs17234657	Chr. 5	513	106
CD	rs1000113	Chr. 5	626	107
T2D	rs12255372	TCF7L2	745	510
T2D	rs12243326	TCF7L2	746	520
CD	rs17221417	NOD2	866	107
AF	rs10033464	Chr. 4q25	1046	143
CD	rs2542151	PTPN22	1104	107
MS	rs2104286	IL2RA	2133	61
MS	rs6897932	IL7RA	2263	61
T2D	rs10811661	CDKN2B	2406	534
T2D	rs8050136	FTO	2569	533
T2D	rs5219	KCNJ11	2792	533
T2D	rs5215	KCNJ11	2908	527
T2D	rs4402960	IGF2BP2	3111	527

Figure 2. Odds Ratios for Comparisons of Cases versus Controls for Each SNP Evaluated

These are ordered by the number of cases required for replication ("number needed" column), calculated from the previously reported odds ratio (OR_{PR}, red square; see text). The blue diamonds indicate the point estimate of the allelic OR derived from the present analysis. The error bars indicate the confidence interval of the allelic OR derived from the present analysis. This analysis used only definite cases in which European ancestry had been assigned. AF, atrial fibrillation; CD, Crohn disease; MS, multiple sclerosis; RA, rheumatoid arthritis; T2D, type 2 diabetes.

information from multiple, interacting, trained physicians when available. Similarly, controls may also represent a more definite phenotype than those in traditional research cohorts because there is an average of 6.6 yrs of follow up in the EMR. In our study, replication of genotype-phenotype associations was slightly improved by incorporation of definite + probable phenotypes in rheumatoid arthritis, but the sample sizes are small.

In this experiment, we did not replicate any association with an $OR_{PR} < 1.25$ or an estimated number of required cases > 1000. Because it was undertaken early in the growth of the biobank, the study was anticipated to be underpowered to assess many of the analyses attempted, given the prevalence of the diseases of interest in the first 10,000 samples accrued. Our failure to replicate could also have arisen because these associations could be important only in certain populations. This highlights one of the advantages of large DNA resources such as BioVU: simple extrapolation indicates that with the current size of the biobank, 18/21 tests of replication would be adequately powered. It is noteworthy that the OR point estimates for all 21 associations evaluated were in the expected direction. Larger populations may also permit discovery of new genetic associations.

However, we successfully replicated genotype-phenotype associations that were underpowered. Although this could reflect simple statistical variation for a few SNPs, it was observed in multiple analyses for multiple diseases. It is conceivable that that the phenotype criteria used here result in a more stringently defined case than in the original studies that identified the genotype-phenotype association. In addition, other studies have used controls drawn from apparently healthy populations,[16] and to the extent that these include subjects who actually have disease, the EMR-based approach that we have used may be superior. It is also possible that the risk alleles are enriched in the population studied, although we observed this phenomenon with multiple diagnoses. Studies in other data sets will be required to address this issue and are a goal of the National Human Genome Research Institute's eMERGE Network.[29]

A long-term goal of BioVU and similar resources[30] is to provide a platform for evaluating and overcoming barriers to incorporation of genomic and other high-dimensional data into clinical medicine. One challenge is to determine the added value of a particular genotype or set of genotypes in clinical care. To address this question, data sets much larger than those ordinarily accrued into clinical trials may be required.[31] Thus, EMR-based biobanks like BioVU may be not only useful but in fact indispensible in advancing this field. Moreover, as this experiment demonstrates, EMR-based phenotyping can rapidly generate large numbers of subjects across multiple diseases. Thus, the approach that we describe ultimately provides a platform for assessment and validation of genotype-phenotype associations in clinical practice. In addition, the method provides an opportunity to generate a closed loop: as health care information accumulates, genotype-phenotype associations will become increasingly well defined, ultimately identifying common genotype variants that are useful in clinical medicine.

Appendix: Selection of Cases and Controls

General Approach

Phenotype-selection algorithms used a combination of queries of structured billing codes and unstructured "natural language" clinical notes. Most algorithms combined a search for disease codes taken from International Classification of Diseases, version 9-CM (ICD-9), and procedure codes from Current Procedural Terminology (CPT) billing records, with textual searches for medication names used to treat the disease. For all text searches, we included synonyms, abbreviations, acronyms, and common misspellings for all terms (including generic and brand names for medications), assisted by standardized vocabularies such as the Unified Medical Language System (UMLS; see Web Resources) and natural language processing tools such as the KnowledgeMap concept identifier.[32]

We required that control records have "minimum content information," defined as an inpatient history and physical admission document or comprehensive outpatient clinic note that included nonempty medication and past medical history sections.

We removed "family medical history" sections from all clinical notes prior to processing.[33]

The algorithms considered inpatient admission notes, progress notes, and discharge summaries; all outpatient clinic notes (> 97% of all outpatient encounters produce notes available in electronic formats since about 2001); all problem lists (these include key diagnoses and procedures, and allergy and medication lists); and the cardiologist-generated electrocardiogram (ECG) impressions.

For Crohn disease, many records included codes for both ulcerative colitis and Crohn disease (e.g., a patient initially thought to have ulcerative colitis who later has a biopsy confirming Crohn disease). To differentiate them, the algorithm also used the ratio of billing codes for each disease.

In each case, content experts were consulted to identify potentially overlapping diseases (such as other autoimmune diseases for rheumatoid arthritis, Crohn disease, and multiple sclerosis) that we excluded from both cases and controls.

Each algorithm was validated and adjusted to achieve target positive and negative predictive values, as described in the text. The final algorithms used to select cases and controls are described in further detail below.

Atrial Fibrillation

For all cases, we considered atrial fibrillation and atrial flutter as similar entities. We excluded all patients who had received heart transplants (identified by CPT codes; Table A1).

Table A1. ICD-9 and CPT Codes Used for Excluding Heart Transplant

Description	ICD-9/CPT Code
Heart replaced by transplant	V42.01
Anesthesia for heart transplant or heart/lung transplant	580
Complications of transplanted heart	996.83
Heart-lung transplant with recipient cardiectomy-pneumonectomy	33935
Heart transplant, with or without recipient cardiectomy	33945

Definite cases: To identify definite cases, we required a cardiologist diagnosis of atrial fibrillation as identified by a natural language processing tool from the unstructured free text of the "ECG impression;" i.e., an ECG with an official interpretation of atrial fibrillation. These were identified by first taking all ECG impressions (n = 14,569) and processing them with the KnowledgeMap concept identifier. This tool[34] maps unstructured free text to standardized biomedical concepts with their assertion or negation status (e.g., "no atrial fibrillation" becomes "C0004238 Atrial Fibrillation, status: negated" in which "C0004238" represents a unique identifier for the concept of "atrial fibrillation" and its synonyms). There were only two negated atrial fibrillation or flutter concepts, both in records that had prior ECGs indicating atrial fibrillation (e.g., "compared with prior ECG, atrial fibrillation has resolved").

Controls: To be a control, a record had to meet all of the conditions below:

- Contain at least one ECG whose impression does not mention atrial fibrillation (or synonym).
- Contain no ICD-9 codes representing atrial flutter or atrial fibrillation (Table A2).
- Contain no free-text matches for atrial fibrillation or synonyms.
- Contain no free-text references (including synonyms) to: direct-current cardioversion, atrial tachycardia or multifocal atrial tachycardia, atrioventricular nodal ablation.

Table A2. ICD-9 Codes for Atrial Fibrillation or Atrial Flutter

Description	ICD-9 Code
Atrial fibrillation	427.31
Atrial fibrillation and flutter	427.3
Atrial flutter	427.32

Crohn Disease

Definite cases: To be considered a definite case, a record had to contain all of the following:

- At least one ICD-9 code for Crohn disease (555.*). If also containing an ICD-9 code for ulcerative colitis (556.*), we required that the ratio of Crohn disease ICD-9 codes to ulcerative colitis ICD-9 codes was ≥ 2.
- At least one medication used to treat Crohn disease, such as: balsalazide, mesalamine, sulfasalazine, ciprofloxacin, levofloxacin, metronidazole, rifaximin, prednisone, budesonide, azathioprine, mercaptopurine, methotrexate, infliximab, adalimumab, certolizumab, natalizumab.

Controls: These were defined as a record with "minimum content information" described above, plus none of the following:

- Any free-text references to key autoimmune diseases or inflammatory bowel disease: rheumatoid arthritis, Felty syndrome, juvenile arthritis, lupus, inflammatory bowel disease, Crohn disease, ulcerative colitis, reactive arthritis, sarcoidosis, ankylosing spondylitis, Hashimoto thyroiditis, polymyositis, dermatomyositis, chronic lymphocytic thyroiditis, autoimmune thyroid disease, Graves disease, Raynaud disease, multiple sclerosis.
- ICD-9 codes indicating another autoimmune diseases or inflammatory bowel disease (Table A3).

Table A3. ICD-9 Codes Indicating Another Autoimmune Disease or Inflammatory Bowel Disease

Description	ICD-9 Code
Rheumatoid arthritis and other inflammatory polyarthropathies	714.*
Discoid lupus erythematosus of eyelid	373.34
Lupus erythematosus	695.4
Systemic lupus erythematosus	710.0
Systemic sclerosis	710.1
Sjogren disease	710.2
Dermatomyositis	710.3
Polymyositis	710.4
Regional enteritis of small intestine	555.*
Sarcoidosis	135
Psoriasis and similar disorders	696
Psoriatic arthropathy	696.0
Other psoriasis and similar disorders excluding psoriatic arthropathy	696.1
Other psoriasis and similar disorders	696.8
Reiter disease	099.3
Palindromic rheumatism	719.3
Ankylosing spondylitis	720.*
Thoracic spondylosis without myelopathy	721.2
Lumbosacral spondylosis without myelopathy	721.3
Hashimoto thyroiditis	245.2
Toxic diffuse goiter	242.0
Myasthenia gravis	358.0*
Neonatal myasthenia gravis	775.2
Raynaud syndrome	443
Reiter disease	099.3
Multiple sclerosis	340
Demyelinating disease of the central nervous system, unspecified	341.9
Irritable bowel disease	564.1
Ulcerative enterocolitis	556.*

Multiple Sclerosis

Definite cases: To be considered a definite case, a record had to meet one of the following two case definitions:

- Case definition 1: Presence of an ICD-9 code for multiple sclerosis (340).
- Case definition 2: Any record matching all of the following:
  - One of the following ICD-9 codes: 341.9, demyelinating disease of the central nervous system, unspecified; 323.9, transverse myelitis.
  - Any of the following medications: interferon-β 1a, interferon-β 1b, glatiramer, natalizumab.
  - Text match of "multiple sclerosis."
  - No potentially overlapping autoimmune diseases by ICD-9 code (Table A4).

Possible cases: To be considered a possible case, a record had to contain all of the following:

- Text match of "multiple sclerosis" in the clinical record.
- Any one of the following ICD-9 codes: other demyelinating diseases of central nervous system;

demyelinating disease of the central nervous system, unspecified; optic neuritis.

- No potentially overlapping autoimmune diseases by ICD-9 code (Table A4).

Because of the small number of cases of multiple sclerosis, we manually reviewed all cases and analyzed them with and without the autoimmune disease exclusions (those with potentially overlapping autoimmune diseases were referred to as "probable cases").

Table A4. ICD-9 Codes Indicating Another Autoimmune Disease

Description	ICD-9 Code
Rheumatoid arthritis and other inflammatory polyarthropathies	714.*
Discoid lupus erythematosus of eyelid	373.34
Lupus erythematosus	695.4
Systemic lupus erythematosus	710.0
Systemic sclerosis	710.1
Sjogren disease	710.2
Dermatomyositis	710.3
Polymyositis	710.4
Regional enteritis of small intestine	555.*
Sarcoidosis	135
Psoriasis and similar disorders	696
Psoriatic arthropathy	696.0
Other psoriasis and similar disorders excluding psoriatic arthropathy	696.1
Other psoriasis and similar disorders	696.8
Reiter disease	099.3
Palindromic rheumatism	719.3
Ankylosing spondylitis	720.*
Thoracic spondylosis without myelopathy	721.2
Lumbosacral spondylosis without myelopathy	721.3
Hashimoto thyroiditis	245.2
Toxic diffuse goiter	242.0
Myasthenia gravis	358.0*
Neonatal myasthenia gravis	775.2
Raynaud syndrome	443

Controls: To be considered a control, a record had to contain none of the following:

- Text match for the string "multiple sclerosis."
- A multiple sclerosis ICD-9 code (340, 341.8, 341.9, or 377.3).
- A multiple sclerosis medication.
- Any free-text references to key autoimmune diseases: rheumatoid arthritis, Felty syndrome, juvenile rheumatoid arthritis, lupus, inflammatory bowel disease, Crohn disease, ulcerative colitis, sarcoidosis, ankylosing spondylitis, Hashimoto thyroiditis, reactive arthritis, polymyositis, dermatomyositis, chronic lymphocytic thyroiditis, autoimmune thyroid disease, Graves disease, Raynaud disease, multiple sclerosis.

Rheumatoid Arthritis

Definite cases: These were defined as any record that met all of the following criteria:

- Contains a rheumatoid arthritis ICD-9 code (Table A5).

Table A5. ICD-9 Codes for Rheumatoid Arthritis

Description	ICD-9 Code
Rheumatoid arthritis and other inflammatory polyarthropathies	714
Rheumatoid arthritis	714.0
Felty syndrome	714.1
Other rheumatoid arthritis with visceral or systemic involvement	714.2

- Contains a rheumatoid arthritis medication (any of the following): methotrexate, sulfasalazine, minocycline, hydroxychloroquine, adalimumab, etanercept, infliximab, gold, azathioprine, rituximab, anakinra, abatacept, leflunomide.
- Contains a text match for "rheumatoid arthritis" in any clinical note.
- Does not contain any of the following autoimmune diseases or inflammatory arthritides, by ICD-9 code (Table A6) or by text match: juvenile rheumatoid arthritis, inflammatory osteoarthritis, reactive arthritis.

As with multiple sclerosis, we analyzed rheumatoid arthritis cases with and without the autoimmune disease exclusions. Those with potentially overlapping autoimmune diseases were referred to as "probable cases."

Table A6. ICD-9 Codes Indicating Other Autoimmune Diseases or Inflammatory Arthritides

Description	ICD-9 Code
Reiter disease	099.3
Sarcoidosis	135
Toxic diffuse goiter	242.0
Hashimoto thyroiditis	245.0
Gouty arthropathy	274.0
Multiple sclerosis and other demyelinating diseases	340, 341.9, 323.9

(*Continued on next page*)

Table A6. ***Continued***

Description	ICD-9 Code
Myasthenia gravis	358.0*, 775.2
Raynaud syndrome	443.0
Crohn disease	555.*
Ulcerative colitis	556.*
Irritable bowel syndrome	564.1
Lupus	695.4,710.0, 373.34
Psoriasis	696.*
Systemic sclerosis, Sjogren disease, and polymyositis	710.1,710.2. 710.3, 710.4
Juvenile rheumatoid arthritis	714.3*
Osteoarthrosis	715.*
Palindromic rheumatism	719.*
Ankylosing spondylitis and other spondylosis	720.*, 721.2, 721.3
Rheumatism, unspecified and fibrositis	729.0

Controls: These were defined as any record that <u>did not</u> contain any of the following:

- Any ICD-9 code for rheumatoid arthritis, autoimmune diseases, or other inflammatory arthritides (Table A7).

Table A7. ICD-9 Code for Rheumatoid Arthritis, Autoimmune Diseases, or Other Inflammatory Arthritides

Description	ICD-9 Code
Reiter disease	099.3
Sarcoidosis	135
Toxic diffuse goiter	242.0
Hashimoto thyroiditis	245.0
Gouty arthropathy	274.0
Multiple sclerosis and other demyelinating diseases	340, 341.9, 323.9
Myasthenia gravis	358.0*, 775.2
Raynaud syndrome	443.0
Crohn disease	555.*
Ulcerative colitis	556.*
Irritable bowel syndrome	564.1
Lupus	695.4, 710.0, 373.34
Psoriasis	696.*
Systemic sclerosis, Sjogren disease, and polymyositis	710.1, 710.2. 710.3, 710.4
Rheumatoid arthritis and other inflammatory polyarthropathies	714.*
Osteoarthrosis	715.*
Palindromic rheumatism	719.*
Ankylosing spondylitis and other spondylosis	720.*, 721.2, 721.3
Rheumatism, unspecified and fibrositis	729.0

- Any of the following text in clinical notes: lupus, inflammatory bowel disease, Crohn disease, ulcerative colitis, multiple sclerosis, transverse myelitis, progressive systemic sclerosis, scleroderma, acrosclerosis, dermatomyositis, polymyositis, sarcoidosis, psoriasis / psoriatic arthritis, arthritis, osteoarthritis / degenerative joint disease, reactive arthritis, Sjogren disease, rheumatism, ankylosing spondylitis, Hashimoto thyroiditis, chronic lymphocytic thyroiditis, autoimmune thyroid disease, Graves disease, myasthenia gravis, Raynaud disease.

Type 2 Diabetes

We adapted the type 2 diabetes algorithm designed by William Lowe, Abel Kho, and Wendy Wolf at Northwestern University as part of the eMERGE Network to identify patients at Vanderbilt. Notably, ~20% of the records identified as type 2 diabetes cases also contained diagnostic codes for type 1 diabetes. Manual review (described in the main text) of 50 of these cases revealed that all had type 2 diabetes.

Definite cases:

- Any record including a type 2 diabetes ICD-9 code (Table A8).
- A noninsulin hypoglycemic medication (Table A9).

Controls:

- No type 2 diabetes ICD-9 codes (Table A8).
- No impaired glucose ICD-9 codes (Table A9).
- No family history of diabetes (including type 1, type 2, or unspecified, as identified by keyword searches of family history sections from clinical notes and problem lists), because patients with a family history of diabetes are more likely to develop diabetes in the future (and thus end up being cases).
- No abnormal labs: glucose < 110 mg/dl, hemoglobin A1c $< 6.0\%$.

Table A8. ICD-9 Codes Used for Defining Type 2 Diabetes Cases

Description	ICD-9 Code
Diabetes II with other coma	250.30
	250.32
Diabetes II with hyperosmolarity	250.20
	250.22

Table A8. *Continued*

Description	ICD-9 Code
Diabetes II with unspecified complication	250.90
	250.92
Diabetes II with other unspecified manifestation	250.80
	250.82
Diabetes II with peripheral circulatory disorder	250.70
	250.72
Diabetes II with neurological manifestations	250.60
	250.62
Diabetes II with ophthalmic manifestations	250.50
	250.52
Diabetes II with renal manifestations	250.40
	250.42
Diabetes II without mention of complication	250.00
	250.02

Table A9. ICD-9 Code Exclusions for Type 2 Diabetes Controls

Description	ICD-9 Code
Impaired fasting glucose	790.21
Impaired oral glucose tolerance test	790.22
Abnormal glucose, not otherwise specified	790.29
Glycosuria	791.5
Gestational diabetes	648.*
Dysmetabolic syndrome	277.7
Diabetes—asymptomatic	790.29
Diabetes (all)	250.*
Renal glycosuria	271.4

Supplemental Data

Supplemental Data include four tables and can be found with this article online at http://www.ajhg.org.

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Web Resources

The URLs for data presented herein are as follows:

Electronic Medical Records and Genomics (eMERGE) Network, http://www.gwas.net

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/

Unified Medical Language System, http://www.nlm.nih.gov/pubs/factsheets/umls.html

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