Integrating precision medicine in the study and clinical treatment of a severely mentally ill person

Background: In recent years, there has been an explosion in the number of technical and medical diagnostic platforms being developed. This has greatly improved our ability to more accurately, and more comprehensively, explore and characterize human biological systems on the individual level. Large quantities of biomedical data are now being generated and archived in many separate research and clinical activities, but there exists a paucity of studies that integrate the areas of clinical neuropsychiatry, personal genomics and brain-machine interfaces. *Methods*: A single person with severe mental illness was implanted with the Medtronic Reclaim® Deep Brain Stimulation (DBS) Therapy device for Obsessive Compulsive Disorder (OCD), targeting his nucleus accumbens / anterior limb of the internal capsule. Programming of the device and psychiatric assessments occurred in an outpatient setting for over two years. His genome was sequenced and variants were detected in the Illumina Whole Genome Sequencing Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory. *Results*: We report here the detailed phenotypic characterization, clinical-grade whole genome sequencing (WGS), and two-year outcome of a man with severe OCD treated with DBS. Since implantation, this man has reported steady improvement, highlighted by a steady decline in his Yale-Brown Obsessive Compulsive Scale (YBOCS) score from ~38 to a score of ~25. A rechargeable Activa RC neurostimulator battery has been of major benefit in terms of facilitating a degree of stability and control over the stimulation. His psychiatric symptoms reliably worsen within hours of the battery becoming depleted, thus providing confirmatory evidence for the efficacy of DBS for OCD in this person. WGS revealed that he is a heterozygote for the p.Val66Met variant in BDNF, encoding a member of the nerve growth factor family, and which has been found to predispose carriers to various psychiatric illnesses. He carries the p.Glu429Ala allele in methylenetetrahydrofolate reductase (MTHFR) and the p.Asp7Asn allele in ChAT, encoding choline O-acetyltransferase, with both alleles having been shown to confer an elevated susceptibility to psychoses. We have found thousands of other variants in his genome, including pharmacogenetic and copy number variants. This information has been archived and offered to this person alongside the clinical sequencing data, so that he and

others can re-analyze his genome for years to come. *Conclusions*: To our knowledge, this is the first study in the clinical neurosciences that integrates detailed neuropsychiatric phenotyping, deep brain stimulation for OCD and clinical-grade WGS with management of genetic results in the medical treatment of one person with severe mental illness. We offer this as an example of precision medicine in neuropsychiatry including brain-implantable devices and genomics-guided preventive health care.

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Introduction

There is a substantial body of literature that highlights the breadth of human phenotypic diversity[1-12]. And yet, despite a body of scientific work demonstrating significant contributions from genetic and environmental heterogeneity to this diversity, relatively broad phenotypic categorizations still dominate traditional medical classifications[13-17]. Furthermore, over the past 50 years, psychiatry, and medicine in general, has shifted its focus toward providing pre-market proof of the overall efficacy and safety of drugs and other interventions in randomized clinical trials involving hundreds (and sometimes thousands) of people, despite the existence of phenotypic heterogeneity and variable expressivity in nearly every person and every disease over time[6,8,9,18]. This course of affairs was brought about by a large confluence of societal factors, including safety concerns stemming from numerous biomedical transgressions over the years [19], including the indiscriminate use of lobotomy in the field of psychiatry[20,21]. However, there is some evidence suggesting that we might be now undergoing a transformation of the medical world[22,23], with a return to individual-focused medical care and to the realization that each individual is truly unique, influenced by their own genetic and environmental factors[3,5,24-26].

Along these lines, deep brain stimulation (DBS) has emerged as a relatively safe and reversible neurosurgical technique that can be used in the clinical treatment of traditionally treatment resistant psychiatric disorders. DBS enables the adjustable and stable electrical stimulation of targeted brain structures. A recent paper by Hoflich et al[27] notes variability in treatment outcomes for DBS patients, which is likely due to variable responses to differences in targeted stimulation regions and in post-operative stimulation parameters. Both sources of variation, the authors note, will effect the stimulation of different brain tissue fibers having different anatomical and functional connections. Furthermore, the authors suggest that not every target will be suitable for every person, as there exists a large degree of inter-individual variability of brain region activation during a reward task in healthy volunteers, and suggest that future work could (and should) focus on developing surgical plans based on individual-specific activations, functional connectivity and/or tractography. This work exemplifies the large degree of clinically relevant biological variability that exists in terms of individual clinical characteristics.

Ongoing clinical trials testing the "Effectiveness of Deep Brain Stimulation for Treating People With Treatment Resistant Obsessive-Compulsive Disorder"[28] detail the below exclusion criteria:

- current or past psychotic disorder,
- a clinical history of bipolar mood disorder, and/or
- an inability to control suicide attempts, imminent risk of suicide in the investigator's judgment, or a history of serious suicidal behavior, which is defined using the Columbia-Suicide Severity Rating Scale (C-SSRS) as either: one or more actual suicide attempts in the 3 years before study entry with the lethality rated at 3 or higher, or one or more interrupted suicide attempts with a potential lethality judged to result in serious injury or death.

Unfortunately, these study criteria exclude the most severe cases of OCD, as many people with severe OCD also have severe depression, usually with passive (and sometimes active) suicidal ideation[29-31]. Obsessions and compulsions can be quite severe, with very poor insight, sometimes to a delusional or psychotic degree, and there can also be co-occurring psychoses in any individual. Each person is to some

degree unique in his or her psychiatric presentation, and a tailored evaluation schema may be more effective in clinical treatment. Indeed, categorical thresholds for clinical trials and/or general psychiatric treatment lack the continuous gradation that would otherwise enable a high degree of treatment precision for any one person. Due in part to these substantial hurdles, there are unfortunately very few detailed descriptions of the efficacy of DBS for OCD, with the number of published case studies on the efficacy of DBS for OCD covering upwards of ~100 people [32-47]. This is really quite small, given that there are 6-7 billion people on this planet, with some estimates of the prevalence of OCD ranging from 0.4-1.2% in the community and perhaps more in military veterans [48].

There has, in parallel, been an explosive growth in exome and whole genome sequencing (WGS) [25], led in part by dramatic cost reductions. The same is true for genotyping microarrays, which are becoming increasingly denser with various markers while maintaining a relatively stable cost [49]. In the medical world, WGS has led to the discovery of the genetic basis of Miller Syndrome [50] and in another instance, it was used to investigate the genetic basis of Charcot-Marie-Tooth neuropathy [51], alongside a discussion of the 'return of results' [52]. In 2011, the diagnosis of a pair of twins with dopa (3,4-dihydroxyphenylalanine) responsive dystonia (DRD; OMIM #128230) and the discovery through WGS that they carried compound heterozygous mutations in the SPR gene encoding sepiapterin reductase led to supplementation of l-dopa therapy with 5-hydroxytryptophan, a serotonin precursor, resulting in clinical improvements in both twins [53].

As the cost of WGS decreases, evidence is emerging that exon capture and sequencing only achieves a high depth of sequencing coverage in about 90% of the exons, whereas WGS does not involve a capture step and thus obtains better coverage on >95% of all exons in the genome. Of course, even the definition of the exome is a moving target, as the research community is constantly annotating and finding new exons not previously discovered [54,55], and therefore WGS is a much more comprehensive way to assess coding and non-coding regions of the genome. Given that WGS can impact clinical care, it is now a matter of economics and feasibility in terms of whether and when WGS will be adopted widely in a clinical setting [25,56].

In our own efforts to push forward the field of precision medicine, we are studying individuals and families with a diverse range of illnesses. We report here one effort to integrate the areas of clinical neuropsychiatry, brain machine interfaces and personal genomics in the individualized care of one person. We evaluate and treat an individual with DBS for treatment refractory OCD and also gauge the feasibility and usefulness of the medical integration of genetic data stemming from whole genome sequencing. To date, there have been relatively few reports on studies detailing the effective application of DBS for OCD; we report here one such study.

Methods

Ethics compliance

Research was carried out in compliance with the Helsinki Declaration. The corresponding author (GJL) conducted all clinical evaluations and he is an adult psychiatry and child/adolescent psychiatry diplomate of the American Board of Psychiatry and Neurology. GJL obtained IRB approval #00038522 at the University of Utah in 2009-2010 to evaluate candidates for surgical implantation of the Medtronic Reclaim® DBS Therapy for OCD, approved under a Humanitarian Device Exemption (HDE) for people with chronic, severe, treatment-resistant OCD[57]. The interdisciplinary treatment team consisted of one psychiatrist (GJL), one neurologist and one neurosurgeon. Implantation ultimately occurred on a clinical basis at another site. Written consent was obtained for phenotyping and whole genome sequencing through Protocol #100 at the Utah Foundation for Biomedical Research, approved by the Independent Investigational Review Board, Inc. Informed and written consent was also obtained using the Illumina Clinical Genome Sequencing test consent form, which is a clinical test ordered by the treating physician, G.J.L.

Evaluation and recruitment for DBS for treatment-refractory OCD

GJL received training regarding DBS for OCD at a meeting hosted by Medtronic in Minneapolis, Minnesota, in September 2009. The same author attended a Tourette Syndrome Association meeting on DBS for Tourette Syndrome, Miami, Florida, in December 2009. Approximately ten candidates were evaluated over a one-year period in 2010. The individual discussed herein received deep brain stimulation surgery at another site, and then returned for follow-up with GJL. Another psychiatrist, author RR, provided ongoing consultation throughout the course of this study. Although other candidates have since returned for follow-up (with GJL), no others have been surgically treated.

CLIA Whole Genome Sequencing and the Management of Results from sequencing data

Whole genome sequencing was ordered on this individual as part of our ongoing effort to implement precision medicine in the diagnosis, treatment, and preventive care for individuals. His genome was sequenced in the Illumina Clinical Services Laboratory (CLIA-certified, CAP-accredited) as part of the TruSight Individual Genome Sequencing (IGS) test, a whole-genome sequencing service using Illumina's short- read sequencing technology[58]. Although clinical genome sequencing was ordered by GJL on a clinical basis (thus not requiring IRB approval), the clinical phenotyping and collection of blood and saliva for other research purposes was approved by the Institutional Review Board (iIRB) (Plantation, Florida) as part of a study protocol at the Utah Foundation for Biomedical Research (UFBR). Consistent with laboratory-developed tests, WGS has not been cleared or approved by the U.S. Food and Drug Administration[59]. The entire procedure included barcoded sample tracking of the blood collected by GJL from this person, followed by DNA isolation and sequencing in the Illumina CLIA lab. Data statistics are summarized in Supplemental Fig. S1. For the bioinformatics analyses, Illumina utilized the internal assembler and variant caller CASAVA (short for Consensus Assessment of Sequence And VAriation). Reads were mapped to the Genome Reference Consortium assembly GRCh37. Data for sequenced and assembled genomes was provided on one hard drive, formatted with the NTFS file system and encrypted using the open source cross platform TrueCrypt software (www.truecrypt.org) and the Advanced Encryption Standard (AES) algorithm (Federal Information Processing Standards Publication 197).

Genotyping array data was generated in parallel of the CLIA whole genome sequencing, using the Illumina HumanOmni2.5-8 bead chip. The encrypted hard drive contains several files, including a "genotyping folder" within which there is a genotyping report in a text-based tab-delimited format (see Supplemental File S1). See Supplemental File 11 for more details on the genotyping array data.

Insertions, deletions and structural alterations are not validated variant types in the Illumina Clinical Services Laboratory. Insertions and deletions provided in the gVCF file are for investigative or research purposes only. A medical report and the raw genomic data were provided back to the ordering physician (GJL) on an encrypted hard drive as part of the Illumina Understand your Genome Symposium, held in October 2012, which included the clinical evaluation of 344 genes (see Supplemental File S2 and S3)[60].

To perform more comprehensive downstream analyses using a greater portion of the genomic data, all of the variants that were detected by the Illumina CLIA WGS pipeline were imported and analyzed within the Omicia Opal web-based clinical genome interpretation platform (Supplemental Fig. S5), version 1.5.0[61]. The Omicia system annotates variants and allows for the identification and prioritization of potentially deleterious alleles. Omicia Scores, which are computationally derived estimates of deleteriousness, were calculated by using a decision-tree based algorithm, which takes as input the Polyphen, SIFT, MutationTaster and PhyloP score(s), and derives an integrative score between 0 and 1. Receiver operating characteristic (ROC) curves are plotted for that score based on annotations from HGMD. For further details on the method and the program see the Supplemental File S11 and www.omicia.com. The AssureRx Health, Inc. annotation and analysis pipeline was used to further annotate variants (see Supplemental File S11 for more detailed methods).

We also applied a recently published method, ERDS (Estimation by Read Depth with SNVs) version

1.06.04[62], in combination with genotyping array data, to generate a set of CNV calls. ERDS starts from read depth information inferred from BAM files, but also integrates other information including paired end mapping and soft-clip signature, to call CNVs sensitively and accurately. We collected deletions and duplications that were >200 kb in length, with confidence scores of >300. CNVs that were detected by the ERDS method were visually inspected by importing and visualizing the read alignment data in the Golden Helix Genome Browser, version 1.1.1. CNVs were also independently called from Illumina HumanOmni2.5-8v1 genotyping array data. Array intensities were imported and analyzed within the Illumina GenomeStudio software suite, version 1.9.4. LogR values were exported from GenomeStudio and imported into Golden Helix SVS, version 7.7.5. A Copy Number Analysis Method (CNAM) optimal segmentation algorithm was used to generate a list of putative CNVs, which was then restricted to include only CNVs that were >200kb in length with average segment LogR values of > 0.15 and < -0.15 for duplications and deletions, respectively. LogR and covariate values were plotted and visually inspected at all genomic locations where the CNAM method detected a CNV. CNVs that were simultaneously detected by both methods (ERDS and CNAM) were considered to be highly confident CNVs. Highly confident CNVs were, again, visually inspected within Golden Helix Genome Browser to further eliminate any artefactual CNV calls.

A board-certified genetic counselor was consulted by GJL prior to returning results, and all therapy and counseling was provided by GJL.

Results

Pertinent clinical symptoms and treatment

A 37-year old man and U.S. veteran (here named with pseudonymous initials M.A.) was evaluated by GJL in 2010 for severe, treatment-refractory obsessive compulsive disorder (OCD), which is an illness that can be quite debilitating[63]. M.A. had a lifelong history of severe obsessions and compulsions, including contamination fears, scrupulosity, and the fear of harming others, with much milder symptoms in childhood that got much worse in his early 20's. His Yale-Brown Obsessive Compulsive Scale (YBOCS)[64,65] ranged from 32-40, indicating extremely severe OCD. Perhaps the worst period of OCD included a 5-day, near continuous, period of tapping on his computer keyboard as a compulsion to prevent harm from occurring to his family members. M.A. had suffered throughout his life from significant periods of depression with suicidal ideation, and he had attempted suicide at least three times. His prior psychiatric history also includes episodes of paranoia relating to anxieties from his OCD, and he continues to be treated with biweekly injections of risperidone.

His treatment history included over 15 years of multiple medication trials, including clomipramine and multiple SSRIs at high doses, including fluoxetine at 80 mg by mouth daily, along with several attempts with outpatient exposure and ritual prevention (ERP) therapy[66]. M.A. inquired and was evaluated by GJL at the University of Utah and then at two other centers independently offering deep brain stimulation for OCD. One of these centers required (as a condition for eligibility for an ongoing clinical trial) a two-week inpatient hospitalization with intensive ERP, which was documented as improving his YBOCS score to 24 at discharge. He maintains that he actually experienced no improvement during that hospitalization, but rather told the therapists what they wanted to hear, as they were "trying so hard". See the Supplemental File S11 for other clinical details.

The teams at the University of Utah and two other centers declined to perform surgery due to his prior history of severe depression, suicide attempts and possible psychoses with paranoia. Through substantial persistence of M.A. and his family members, a psychiatrist and neurosurgeon at a fourth center decided that he was an appropriate candidate for surgical implantation of the Medtronic Reclaim® DBS Therapy device for OCD, approved under a Humanitarian Device Exemption (HDE) for people with chronic, severe, treatment-resistant OCD[57], and he was implanted in January of 2011 (Fig. 1). The device targets the nucleus accumbens / anterior limb of the internal capsule (ALIC). A detailed account of the surgical procedure can be found in the Supplemental File 11.

Clinical results for DBS for treatment-refractory OCD

After healing for one month, the implanted device (equipped with the Kinetra Model 7428 Neurostimulator) was activated on February 14, 2011, with extensive programming by an outpatient psychiatrist, with bilateral stimulation of the ALIC. Final settings were case positive, contact 1 negative on the left side at 2.0 V, frequency 130 Hz, and pulse width 210 usec, and case positive, contact 5 negative on the right side with identical settings.

Over the next few months, his voltage was increased monthly in increments of 0.2-0.5 V by an outpatient psychiatrist. He returned to one of the author's (GJL) for psychiatric treatment in July 2011, at which time his voltage was set at 4.5 V bilaterally. His depression had immediately improved after the surgery, along with many of his most irrational obsessions, but his YBOCS score still remained in the 35-38 range. From July 2011-December 2011, his voltage was increased bilaterally on a monthly basis in increments of 0.2 V, with steady improvement with his OCD until his battery started to lose charge by December 2011. This caused him considerable anxiety, prompting him to turn off his battery in order to "save battery life", which unfortunately led to a complete relapse to his baseline state in a 24 hour period, which was reversed when he turned the battery back on. The battery was surgically replaced with a rechargeable *Activa RC* neurostimulator battery in January 2012, and the voltage has been increased monthly in 0.1-0.2 V increments until the present time (May 2013).

At every visit, M.A. has reported improvements, with reductions of his obsessions and compulsions, marked by a steady decline in his YBOCS score (Fig. 3). M.A. has started to participate in many activities that he had never previously been able to engage in. This includes: exercising (losing 50 pounds in two years) and volunteering at the church and other organizations. In fact, M.A. started dating and recently became engaged to be married, highlighting his improvement in daily functioning. New issues that M.A. reports are consistent tenesmus, occasional diarrhea (which he can now tolerate despite prior contamination obsessions) and improved vision (going from 20/135 to 20/40 vision, as documented by his optometrist), with him no longer needing to wear glasses. It is unknown whether the DBS implant has contributed to any of these issues. Attempts to add fluoxetine at 80 mg by mouth daily for two months to augment any efficacy from the DBS and ERP were unsuccessful, mainly due to no discernible benefit and prominent sexual side effects. M.A. still receives an injection of 37.5 mg risperidone every two weeks for his past history of psychoses; otherwise, he no longer takes any other medications. There has not been any exacerbation of psychoses in this individual during the two years of treatment with DBS.

CLIA certified Whole Genome Sequencing results

The Illumina WGS clinical evaluation included manual annotation of 344 genes (see Supplemental Fig. S2, Supplemental File S2 and S3), which led to the following conclusion:

> "*No pathogenic or likely pathogenic variants were found in the 344 genes evaluated that are expected to be clinically significant for the patient. The coverage for these 344 genes is at least 99%. Therefore, significant variants could exist that are not detected with this test.*"

The clinical evaluation did, however, identify M.A. as a carrier for a variant (c.734G>A ,p.Arg245Gln) in *PHYH*, which has been associated in the autosomal recessive or compound heterozygote states with Refsum disease, which is an inherited condition that can lead to vision loss, anosmia, and a variety of other signs and symptoms[67]. In silico prediction programs suggest little impact; however, the variant is rare with a 1000 Genomes frequency of ~0.18%. In this regard, it is worth noting that M.A. has always had poor night vision and enlarged pupils, and, as a result of this genetic finding, we met with M.A.'s treatment team at his Veteran's Affair's (V.A.) medical center and learned that he had recently been diagnosed with bilateral cataracts, enlarged pupils, and vision loss. We also learned that M.A.'s mother and maternal grandfather have a history of enlarged pupils with poor vision, and we are currently following up whether this might be related in any way to this particular variant and Refsum disease. This finding is one example of why it is important to archive and re-interpret his genome going forward, as any

number of variants could influence his medical care over the course of his life. To achieve this, one of us (GJL) has previously argued in favor of an analytic-interpretive split in the area of clinical genomics, in which WGS is discrete deliverable clinical unit, allowing for multiple downstream interpretive analyses, by any number of people, including the individual and/or his/her health care providers[59]. We have implemented that model here with M.A. by archiving and offering to him and his health care providers the encrypted hard drive containing his "raw" sequencing data, along with analyzing the data with several downstream pipelines (Fig. 2).

Further downstream analyses identified and prioritized several other potentially clinically relevant variants. Variants that were imported into the Omicia Opal system were filtered to include those that had a high likelihood of being damaging (as defined by an Omicia score > 0.7) and those that have supporting Online Mendelian Inheritance in Man (OMIM; an online database of human genetics and genetic disorders) evidence. We chose to filter based on an Omicia Score of > 0.7 as this value derives a slightly more inclusive list of variants which still cannot be dismissed, but for which we have additional corroborating evidence (i.e., Illumina Genome Network (IGN) validation and annotation). These prioritized variants were further annotated and evaluated by the AssureRx Health, Inc. annotation and analysis pipeline. Prioritized variants are shown in Supplemental File S4 and Supplemental Fig. S3. A longer list of variants, which were required only to have supporting evidence within the OMIM database, is shown in Supplemental File S5. We highlight here some of the findings:

M.A. was found to be a heterozygote for a p.Val66Met change in *BDNF*, which encodes a protein that is a member of the nerve growth factor (NGF) family. The protein is induced by cortical neurons, and is deemed necessary for the survival of striatal neurons in the brain. In drug naïve patients, BDNF serum levels were found to be significantly decreased in OCD patients when compared to controls (36.90 ± 6.42 ng/ml versus 41.59 ± 7.82 ng/ml; p = 0.043)[68], suggesting a link between this protein and OCD. Moreover, a study including 164 proband-parent trios with obsessive-compulsive disorder[69] uncovered significant evidence of an association between OCD and all of the *BDNF* markers that were tested, including the exact variant found here in this person, p.Val66Met. This particular variant has been further studied in a sample of 94 nuclear families[70], which included 94 probands with schizophrenia-spectrum disorders and 282 family members. The results of this study suggest that the p.Val66Met polymorphism may play a role in the phenotype of psychosis. Similar anxiety-related behavioral phenotypes have also been observed among mice and humans having the p.Val66Met variant in BDNF[71]. In humans, the amygdala mediates conditioned fear[72], normally inhibited by 'executive centers' in medial prefrontal cortex[73]. Deep brain stimulation of the pathways between medial prefrontal cortex and the amygdala increased the extinction of conditioned fear in a rat model of OCD[74]. Studies using functional magnetic resonance imaging (fMRI) demonstrate that humans with the p.Val66Met variant exhibit exaggerated activation of the amygdala in response to an emotional stimulus in comparison to controls lacking the variant[75,76]. It is thought that this variant may influence anxiety disorders by interfering with the learning of cues that signal safety rather than threat and may also lessen efficacy of treatments that rely on extinction mechanisms, such as exposure therapy[71]. In this regard, it is interesting to note that this person did indeed obtain very little benefit from exposure therapy prior to surgery.

M.A heterozygously carries the p.Glu429Ala allele in MTHFR, encoding a protein that catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine, and which has been shown to confer an elevated susceptibility to psychoses. Variants in *MTHFR* influence susceptibility to occlusive vascular disease, neural tube defects, colon cancer and acute leukemia. Variants in this gene are associated with methylenetetra-hydrofolate reductase deficiency. In addition, a meta-analysis comparing 1,211 cases of schizophrenia with 1,729 controls found that the MTHFR p.Glu429Ala allele was associated with susceptibility to schizophrenia[77] (odds ratio, 1.19; 95% CI, 1.07- 1.34; p = 0.002). According to the Venice guidelines for the assessment of cumulative evidence in genetic association studies, the *MTHFR* association exhibited a strong degree of epidemiologic credibility[78]. Pharmacogenetic studies have found a consistent association between the MTHFR p.Glu429Ala allele and metabolic disorder in adult, adolescent and children taking

atypical antipsychotic drugs[79,80].

M.A. is heterozygous for a c.19G>A p.Asp7Asn allele in ChAT, encoding choline O-acetyltransferase, which synthesizes the neuro-transmitter acetylcholine (Supplemental Fig. S5). This particular variant (rs1880676) is significantly associated with both risk for schizophrenia in Caucasians (P = 0.002), olanzapine response (P = 0.02) and for other psychopathology (P = 0.03)[81].

M.A. is also heterozygous for the p.Val108Met variant in catechol-O-methyltransferase(COMT), which catalyzes the transfer of a methyl group from S-adenosylmethionine to catecho- lamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine. The minor allele A of this 472G>A variant produces a valine to methionine substitution, resulting in a less thermostable COMT enzyme that exhibits a 3-fold reduction in activity. A substantial body of literature implicates this variant as possibly elevating the risk for various neuropsychiatric disorders in some Caucasian populations but not necessarily in other genetic backgrounds[82-88]. There is some evidence that MTHFR x COMT genotype interactions might also be occurring in M.A. to influence his neuropsychiatric status[89], and the same is true for BDNF x COMT interactions[90].

Pharmacogenetic analyses were performed using the Omicia Opal platform. Pharmacogenetic variants were identified and prioritized by activating the "Drugs and Pharamcology" track within the Opal system and by requiring these variants to have prior evidence within any one of several supporting databases (i.e., OMIM, HGMD, PharmGKB, LSDB and GWAS). Prioritized variants are shown in Supplemental File S6 and Supplemental Fig. S4. A longer, more inclusive list is shown in Supplemental File S7; variants in this file are only required to be detected by the "Drugs and Pharmacology" track in Opal. Variants within Supplemental File S6/S7 were further annotated and analyzed by the AssureRx Health, Inc. pipeline (see Supplemental File S8).

M.A. is homozygous for a p.Ile359Leu change in CYP2C9, and this variant has been linked to a reduction in the enzymatic activity of CYP2C9[91]. *CYP2C9* encodes a member of the cytochrome P450 superfamily of enzymes. Cytochrome P450 proteins are mono-oxygenases, which catalyze many reactions associated with drug metabolism as well as reactions associated with the synthesis of cholesterol, steroids and other lipids[92]. CYP2C9 localizes to the endoplasmic reticulum and its expression is induced by rifampin. CYP2C9 is known to metabolize xenobiotics, including phenytoin, tolbutamide, ibuprofen as well as S-warfarin. Studies identifying individuals who are poor metabolizers of phenytoin and tolbutamide suggest associations between metabolism and polymorphisms found within this gene. *CYP2C9* is located within a cluster of cytochrome P450 genes on chromosome 10[93]. Fluoxetine is commonly used in the treatment of OCD; it has been shown to be as effective as clomipramine and causes less side effects[94,95]. CYP2C9 acts to convert fluoxetine to R-norfluoxetine[96], and so M.A. may not be able to adequately biotransform fluoxetine[97]. However, CYP2C9 does not play a rate-limiting role for other SSRIs or clomipramine. In his own treatment experience, M.A. had no response to an 80 mg daily dose of fluoxetine, although he did experience sexual side effects at that dosage.

The protein encoded by *DPYD* is a pyrimidine catabolic enzyme and it acts as the initial and rate-limiting factor in uracil and thymidine catabolism pathways. M.A. was found to be a carrier of two variants in this gene, p.Ile543Val and p.Arg29Cys, for which he is a heterozygote and homozygote, respectively. Variants within *DPYD* result in dihydropyrimidine dehydrogenase deficiency, an error in pyrimidine metabolism associated with thymine-uraciluria and an increased risk of toxicity in cancer patients receiving 5-fluorouracil chemotherapy. Two transcript variants encoding different isoforms have been described for *DPYD*[98,99].

A copy number variant (CNV) analysis was performed using the estimation by read depth with single-nucleotide variants (ERDS) method[62] in combination with the Golden Helix Copy Number Analysis Method (CNAM) optimal segmentation algorithm applied to Illumina HumanOmni2.5-8v1 genotyping array data. ERDS identified 60 putative CNVs, all of which were visually inspected within the Golden

Helix Genome Browser. Many of the CNVs detected by the ERDS method were found to be located within chromosomal boundary regions and were determined to be false positives due to highly variable read depth in these regions. The CNAM method detected 35 putative CNVs, which were visually inspected by plotting the LogR and covariate values in Golden Helix SVS. Only six CNVs were simultaneously detected by both the ERDS and CNAM methods, and were visually inspected as further confirmation to be included among the set of highly confident CNVs. High-confidence CNVs are shown in Supplemental File S9. To our knowledge, these CNVs have not been previously associated in any way with M.A.'s disease phenotype.

Although we believe in archiving and managing all genetic results and not just a small subset of genes, we did analyze the 57 genes that are currently recommended for "return of results" by the American College of Medical Genetics[100]. These results are shown in Supplemental File S10.

Lastly, in an ongoing effort to develop ways to incorporate genomic data into clinical electronic health records, we collaborated with the team of Karen Eilbeck to convert the data into the GVFclin format (see Supplemental File S12). The Genome variant format (GVF), which uses Sequence Ontology to describe genome variation[101], has been extended for use in clinical applications. This extended file format, called GVFClin[102], adds the necessary attributes to support Health Level 7 compatible data for clinical variants. The GVF format represents genome annotations for clinical applications using existing EHR standards as defined by the international standards consortium: Health Level 7. Thus, GVFclin can describe the information that defines genetic tests, allowing seamless incorporation of genomic data into pre-existing EHR systems. We did contact the physicians and other officials at the U.S. Veterans Affairs office to offer to incorporate these data into the electronic medical record for M.A., but we were informed that the VistA health information system (HIS)[103-106] does not currently have the capability to incorporate any genomic variant data.

Discussion

DBS for treatment-refractory OCD Deep brain stimulation for M.A.'s treatment refractory OCD has provided a quantifiable and significant improvement in the management of his symptoms (Fig. 3). M.A. has regained a quality of life that he had previously not experienced in over a decade, which is highlighted by him participating in regular exercise, working as a volunteer in his local church and becoming engaged to be married, all of which act to illustrate a dramatic improvement in his daily functioning since receiving DBS treatment for his OCD.

One significant aspect of this study is the rechargeable, and hence depleteable, nature of the *Activa RC* neurostimulator battery, which serves to illustrate the efficacy of DBS for OCD for this individual. On one such illustrative occasion, M.A. forgot to take the recharging device on a four-day weekend trip. Once his battery was depleted, all of his symptoms gradually returned to their full level over a ~24 hour period, including severe OCD, depression and suicidality. Since that episode, M.A. always takes his recharging device with him on extended trips, but there have been other such instances in which his battery has become depleted for several hours, with the noticeable and intense return of his OCD symptoms and the cessation of his tenesmus. The electrical stimulation is having a demonstrable effect on his OCD, and these data are complementary to other data-sets involving turning DBS devices off for one week at a time[45].

There are many ethical and regulatory issues relating to deep brain stimulation that have been discussed elsewhere[107-113], and we report here our one positive experience, made possible when the US Food and Drug Administration granted a Humanitarian Device Exemption (HDE) to allow clinicians to use this intervention. The rechargeable nature of the new battery has been reassuring to M.A., as he is able to exert self-control over his battery life, whereas he previously had no control with the original "single-use" battery that must be replaced when the battery depletes (usually at least once annually). We assume that other persons treated with DBS for OCD will likely also start receiving rechargeable batteries. In this regard, it is worth noting that the recent development of an injectable class of cellular-scale

optoelectronics paves the way for implanted wireless devices[114], and we fully expect that there will be more brain-machine neural interfaces used in humans in the future[115-119].

Clinical Whole Genome Sequencing

During our study, we found that M.A. carries at least three alleles that have been associated with neuropsychiatric phenotypes, including variants in *BDNF*, *MTHFR*, and *ChAT* (Table 1). There are, however, still many challenges in showing how any one mutation can contribute toward a clear phenotype, particularly in the context of genetic background and possible environmental influences [120]. Bioinformatics confounders, such as poor data quality [121], sequence inaccuracy, and variation introduced by different methodological approaches[122] can further complicate biological and genetic inferences. Although the variants discussed in the results section of our study have been previously associated with mental disease, we caution that the data presented are not sufficient to implicate any particular mutation as being necessary or sufficient to lead to the described phenotype, particularly given that mental illness results from a complex interaction of any human with their surrounding environment and social support structures. The genetic architecture of most neuropsychiatric illness is still largely undefined and controversial [123-126], and our data also does not allow us to exclude the possibility of polygenic and epistatic modes of inheritance [127-134]. We provide our study as a cautionary one: WGS cannot act as a diagnostic and prognostic panacea, but instead could act to elucidate potential risk factors for some illnesses. There are certainly other variants and/or environmental interactions that have influenced or will influence the clinical course of M.A., and there will likely be many more gene-gene and gene-environment interactions occurring and impacting various phenotypes developing over the course of his life[135-147].

In the context of the incomplete, and sometimes proprietary, nature of human gene mutation databases, it is likely that analyses and medical guidance gleaned from these WGS data will differ from institution to institution. It is therefor important that people be given the opportunity, like with many other traditional medical tests, to obtain "second opinions". For this to be possible, one must accurately describe the contents of short-read sequencing data in terms of the existing electronic medical health standards, so that these data can be incorporated into an electronic medical health record. Accurately describing the contents of next generation sequencing (NGS) results is particularly critical for clinical analysis of genomic data. However, genomics and medicine use different, often incompatible terminologies and standards to describe sequence variants and their functional effects. In our efforts to treat this one person with severe mental illness, we have implemented the GVFclin format for the variants that were discovered during the sequencing of his whole genome (see Supplemental File S12). We hope to eventually incorporate his genetic data into his electronic health record, if and when the VistA health information system (HIS)[103-106] is upgraded to allow entry of such data. We did already counsel M.A. regarding several genetic variants that may be clinically relevant to predisposing him to his psychiatric disorder[148].

There is, however, considerable controversy in the field of medical genetics concerning the return of genetic results to people, particularly in the context of "secondary", "unrelated", "unanticipated" or "incidental" findings stemming from new high-throughput sequencing techniques. Some people worry about returning the results of such tests, due to their concerns regarding clinical utility, and in response have advocated for selectively restricting the returnable medical content. One such set of recommendations has been provided by the American College of Medical Genetics which recently released guidelines in which they recommended the "return of secondary findings" for 57 genes, without detailed guidance for the rest of the genome [149]. These types of recommendations can take a more paternalistic approach in returning test results to people, and generally involve a deciding body of people that can range in size from a single medical practitioner to a committee of experts. We believe that anyone should be able to access and manage their own genome data[150], just like how anyone should be able to own and manage their medical and radiology test results[151], particularly if the testing is performed with suitably appropriate clinical standards in place, i.e. CLIA in America[56,152].

We tend to think that whole genome sequencing will eventually become like many other laboratory tests, without the risks inherent to many surgical procedures and other medical interventions. There is currently an ongoing project in America to collect phenotype and genetic data on one million U.S. veterans[153]. We have readily demonstrated herein that it is possible to sequence the whole genome of a veteran in a CLIA-certified laboratory, so that these results can be offered to this veteran, and we are working now to determine if we can incorporate any of these results into his electronic medical record at the VA. We also note that there are efforts underway to create "a national resource with linked genealogy and phenotypic data: the Veterans Genealogy Project", and the authors of that paper note the potential of linking this with the genetic information obtained via the Million Veteran Program[154].

Conclusions

One can learn a substantial amount from detailed study of particular individuals (for just a small sampling, see[155-162]), and we believe that we are entering an era of precision medicine in which we can learn from and collect substantial data on informative individual cases. Incorporating insights from a range of scientific and clinical disciplines into the study and treatment of any one person is therefore beginning to emerge as a tractable, and more holistic, approach, and we document here what we believe to be the first integration of deep brain stimulation and whole genome sequencing for precision medicine in the evaluation, treatment and preventive care for one severely mentally ill individual, M.A. We have shown that DBS has been successful in aiding in the care and beneficial clinical outcome of his treatment refractory OCD, and we have also demonstrated that it is indeed feasible, given current technologies, to incorporate health information from WGS into the clinical care of one person with severe mental illness, including with the return of these health information to him directly. On a comparative level, deep brain stimulation has thus far been a more direct and effective intervention for his mental illness than anything discovered from his whole genome sequencing, although the detection and preventive care for his bilateral cataracts was brought about by the WGS. Of course, the genomic data would have been more helpful if obtained much earlier in his medical course, as it could have provided guidance on which medications to avoid or to provide in increased doses, such as fluoxetine.

There are still only sparse data on the effectiveness of DBS for treatment refractory OCD, and current trials and treatment criterion make difficult the implementation and application of this technology for people with severe and treatment refractory forms of OCD, despite clinical promise in this realm (as demonstrated here in our own study). There is currently an intense drive toward individualized data-driven medical care, with the field of cancer medicine being the canonical example, as it is no longer enough to say that a person has cancer, as this distinction is uninformative due to the fact that there are many different well defined molecular etiologies of cancer[163]. This allows for more precise and targeted therapy, and we fully expect this to occur in the field of psychiatry as hundreds to thousands of psychiatric illnesses become better defined by more precise, molecular, means. This is of particular interest for brain implantable devices that allow for adjustable treatment, such as DBS, as each person could be individually treated (and perhaps even self-tuned) in a precise way to maximize efficacy.

We have also found that there are still many challenges in incorporating high-throughput genomics data into the medical health record of any individual, given that many electronic medical record systems are not yet fully compatible with these data. There are also other more fundamental difficulties in the application of genomics guided medicine, as the causal influence of any one, or set, of genetic variant is not at all clear in most cases. Many have proposed using WGS or other genomics data in terms of informing health risk profiles at the individual level[164,165], and still others claim that these data lead to a diagnosis in up to 27% of some rare disease cases in which they are used[166]. We find that health information stemming from WGS cannot currently act as a diagnostic and prognostic panacea, particularly in this case of severe mental illness where the genetic architecture of this class of diseases is unknown. We did find, however, that health information stemming from these data were nevertheless immediately useful in the care of this person, as a variant associated with his ophthalmologic phenotype did indeed inform and enrich his care, and we expect that these data will continue to inform his care as our

understandings of human biology and the genetic architecture of disease improves.

Contributions

GJL conceived of the project, conducted psychiatric evaluations, provided clinical care, analyzed data, supervised other data analyses, and wrote the manuscript. JO edited the manuscript extensively and analyzed the data. HF, GH, ESK and MGR analyzed and interpreted the whole genome data. RR leads the Utah Foundation for Biomedical Research. All authors read, commented on, and approved the final manuscript.

Conflicts of Interest

The corresponding author (GJL) has had informal discussions with representatives from Medtronic, Illumina, and Omicia, Inc., but he has not had any formal consulting role, nor received financial compensation or grants from these or any other for-profit companies performing deep brain stimulation, DNA collection or sequencing. GJL does not hold any patents, and he is unaware of any conflicts of interest on his part. Revenue earned by GJL from providing medical care in Utah is currently donated to the Utah Foundation for Biomedical Research for genetics research. ESK and MGR are co-founders and officers of Omicia, Inc., and GH is an employee of Assure Rx, Inc. All authors read and approved of the content in the manuscript.

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References

1 Mayr, E. *What evolution is*. (Basic Books, 2001).
2 Muller, H. J. *Studies in genetics*. (Indiana University Press, 1962).
3 Penrose, L. S. *The biology of mental defect*. [3d rev. and reset edn, (Sidgwick and Jackson, 1963).
4 Stott, R. *Darwin's ghosts : the secret history of evolution*. 1st edn, (Spiegel & Grau, 2012).
5 Ward, O. C. *John Langdon Down, 1828-1896 : a caring pioneer*. (Royal Society of Medicine Press, 1998).
6 Klein, D. F. The loss of serendipity in psychopharmacology. *Jama* **299**, 1063-1065, doi:10.1001/jama.299.9.1063 (2008).
7 Seguin, E. *Idiocy : and its treatment by the physiological method*. (William Wood & Co., 1866).
8 Treffert, D. A. *Islands of genius : the bountiful mind of the autistic, acquired, and sudden savant*. (J. Kingsley, 2010).
9 Solomon, A. *Far from the tree : parents, children and the search for identity*. 1st Scribner hardcover edn, (Scribner, 2012).
10 Weldon, W. F. R. Mendel's laws of alternative inheritance in peas. *Biometrika* **1**, 228-254 (1902).
11 Leroi, A. M. *Mutants : on the form, varieties and errors of the human body*. (HarperCollins, 2003).
12 Darwin, C. & Wilson, E. O. *From so simple a beginning : the four great books of Charles Darwin*. 1st edn, (Norton, 2006).
13 Phillips, J., Frances, A., Cerullo, M. A., Chardavoyne, J., Decker, H. S., First, M. B., Ghaemi, N., Greenberg, G., Hinderliter, A. C., Kinghorn, W. A., LoBello, S. G., Martin, E. B., Mishara, A. L., Paris, J., Pierre, J. M., Pies, R. W., Pincus, H. A., Porter, D., Pouncey, C., Schwartz, M. A., Szasz, T., Wakefield, J. C., Waterman, G. S., Whooley, O. & Zachar, P. The six most essential questions in psychiatric diagnosis: a pluralogue. Part 4: general conclusion. *Philos Ethics Humanit Med* **7**, 14, doi:10.1186/1747-5341-7-14 (2012).
14 Phillips, J., Frances, A., Cerullo, M. A., Chardavoyne, J., Decker, H. S., First, M. B., Ghaemi, N., Greenberg, G., Hinderliter, A. C., Kinghorn, W. A., LoBello, S. G., Martin, E. B., Mishara, A. L., Paris, J., Pierre, J. M., Pies, R. W., Pincus, H. A., Porter, D., Pouncey, C., Schwartz, M. A., Szasz, T., Wakefield, J. C., Waterman, G. S., Whooley, O. & Zachar, P. The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues of utility and alternative approaches in psychiatric diagnosis. *Philos Ethics Humanit Med* **7**, 9, doi:10.1186/1747-5341-7-9 (2012).
15 Phillips, J., Frances, A., Cerullo, M. A., Chardavoyne, J., Decker, H. S., First, M. B., Ghaemi, N., Greenberg, G., Hinderliter, A. C., Kinghorn, W. A., LoBello, S. G., Martin, E. B., Mishara, A. L., Paris, J., Pierre, J. M., Pies, R. W., Pincus, H. A., Porter, D., Pouncey, C., Schwartz, M. A., Szasz, T., Wakefield, J. C., Waterman, G. S., Whooley, O. & Zachar, P. The six most essential questions in psychiatric diagnosis: a

pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med* **7**, 8, doi:10.1186/1747-5341-7-8 (2012).

16 Phillips, J., Frances, A., Cerullo, M. A., Chardavoyne, J., Decker, H. S., First, M. B., Ghaemi, N., Greenberg, G., Hinderliter, A. C., Kinghorn, W. A., LoBello, S. G., Martin, E. B., Mishara, A. L., Paris, J., Pierre, J. M., Pies, R. W., Pincus, H. A., Porter, D., Pouncey, C., Schwartz, M. A., Szasz, T., Wakefield, J. C., Waterman, G. S., Whooley, O. & Zachar, P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med* **7**, 3, doi:10.1186/1747-5341-7-3 (2012).

17 Kawa, S. & Giordano, J. A brief historicity of the Diagnostic and Statistical Manual of Mental Disorders: issues and implications for the future of psychiatric canon and practice. *Philos Ethics Humanit Med* **7**, 2, doi:10.1186/1747-5341-7-2 (2012).

18 Klein, D. F. The flawed basis for FDA post-marketing safety decisions: the example of anti-depressants and children. *Neuropsychopharmacology* **31**, 689-699, doi:10.1038/sj.npp.1300996 (2006).

19 Skloot, R. *The immortal life of Henrietta Lacks*. (Crown Publishers, 2010).

20 El-Hai, J. *The lobotomist : a maverick medical genius and his tragic quest to rid the world of mental illness*. (J. Wiley, 2005).

21 Pressman, J. D. *Last resort : psychosurgery and the limits of medicine*. (Cambridge University Press, 1998).

22 Topol, E. J. *The creative destruction of medicine : how the digital revolution will create better health care*. (Basic Books, 2012).

23 Wu, T. *The master switch : the rise and fall of information empires*. 1st edn, (Alfred A. Knopf, 2010).

24 Bearn, A. G. *Archibald Garrod and the individuality of Man*. (Clarendon Press; Oxford University Press, 1993).

25 Lyon, G. J. & Wang, K. Identifying disease mutations in genomic medicine settings: current challenges and how to accelerate progress. *Genome Med* **4**, 58, doi:10.1186/gm359 (2012).

26 Angrist, M. *Here is a human being : at the dawn of personal genomics*. 1st edn, (Harper, 2010).

27 Hoflich, A., Savli, M., Comasco, E., Moser, U., Novak, K., Kasper, S. & Lanzenberger, R. Neuropsychiatric deep brain stimulation for translational neuroimaging. *Neuroimage* **79**, 30-41, doi:http://dx.doi.org/10.1016/j.neuroimage.2013.04.065 (2013).

28 *ClinicalTrials.gov Identifier: NCT00640133: Effectiveness of Deep Brain Stimulation for Treating People With Treatment Resistant Obsessive-Compulsive Disorder*, <http://clinicaltrials.gov/show/NCT00640133> (2013).

29 Torres, A. R., Ramos-Cerqueira, A. T., Ferrao, Y. A., Fontenelle, L. F., do Rosario, M. C. & Miguel, E. C. Suicidality in obsessive-compulsive disorder: prevalence and relation to symptom dimensions and comorbid conditions. *J Clin Psychiatry* **72**, 17-26; quiz 119-120, doi:10.4088/JCP.09m05651blu (2011).

30 Alonso, P., Segalas, C., Real, E., Pertusa, A., Labad, J., Jimenez-Murcia, S., Jaurrieta, N., Bueno, B., Vallejo, J. & Menchon, J. M. Suicide in patients treated for obsessive-compulsive disorder: a prospective follow-up study. *J Affect Disord* **124**, 300-308, doi:10.1016/j.jad.2009.12.001 (2010).

31 Balci, V. & Sevincok, L. Suicidal ideation in patients with obsessive-compulsive disorder. *Psychiatry Res* **175**, 104-108, doi:10.1016/j.psychres.2009.03.012 (2010).

32 Roh, D., Chang, W. S., Chang, J. W. & Kim, C. H. Long-term follow-up of deep brain stimulation for refractory obsessive-compulsive disorder. *Psychiatry Res* **200**, 1067-1070, doi:10.1016/j.psychres.2012.06.018 (2012).

33 Goodman, W. K. & Alterman, R. L. Deep brain stimulation for intractable psychiatric disorders. *Annu Rev Med* **63**, 511-524, doi:10.1146/annurev-med-052209-100401 (2012).

34 Blomstedt, P., Sjoberg, R. L., Hansson, M., Bodlund, O. & Hariz, M. I. Deep Brain Stimulation in the Treatment of Obsessive-Compulsive Disorder. *World Neurosurg*, doi:10.1016/j.wneu.2012.10.006 (2012).

35 Burdick, A. P. & Foote, K. D. Advancing deep brain stimulation for obsessive-compulsive disorder. *Expert Rev Neurother* **11**, 341-344, doi:10.1586/ern.11.20 (2011).

36 Mian, M. K., Campos, M., Sheth, S. A. & Eskandar, E. N. Deep brain stimulation for obsessive-compulsive disorder: past, present, and future. *Neurosurg Focus* **29**, E10, doi:10.3171/2010.4.FOCUS10107 (2010).

37 Haynes, W. I. & Mallet, L. High-frequency stimulation of deep brain structures in obsessive-compulsive disorder: the search for a valid circuit. *Eur J Neurosci* **32**, 1118-1127, doi:10.1111/j.1460-9568.2010.07418.x (2010).

38 Goodman, W. K., Foote, K. D., Greenberg, B. D., Ricciuti, N., Bauer, R., Ward, H., Shapira, N. A., Wu, S. S., Hill, C. L., Rasmussen, S. A. & Okun, M. S. Deep brain stimulation for intractable obsessive compulsive disorder: pilot study using a blinded, staggered-onset design. *Biol Psychiatry* **67**, 535-542, doi:10.1016/j.biopsych.2009.11.028 (2010).

39 Denys, D., Mantione, M., Figee, M., van den Munckhof, P., Koerselman, F., Westenberg, H., Bosch, A. & Schuurman, R. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Arch Gen Psychiatry* **67**, 1061-1068, doi:10.1001/archgenpsychiatry.2010.122 (2010).

40 Komotar, R. J., Hanft, S. J. & Connolly, E. S., Jr. Deep brain stimulation for obsessive compulsive disorder. *Neurosurgery* **64**, N13, doi:10.1227/01.NEU.0000349645.64376.86 (2009).

41 Jimenez-Ponce, F., Velasco-Campos, F., Castro-Farfan, G., Nicolini, H., Velasco, A. L., Salin-Pascual, R., Trejo, D. & Criales, J. L. Preliminary study in patients with obsessive-compulsive disorder treated with electrical stimulation in the inferior thalamic peduncle. *Neurosurgery* **65**, 203-209; discussion 209, doi:10.1227/01.NEU.0000345938.39199.90 (2009).

42 Denys, D. & Mantione, M. Deep brain stimulation in obsessive-compulsive disorder. *Prog Brain Res* **175**, 419-427, doi:10.1016/S0079-6123(09)17527-1 (2009).

43 Burdick, A., Goodman, W. K. & Foote, K. D. Deep brain stimulation for refractory obsessive-compulsive disorder. *Front Biosci* **14**, 1880-1890 (2009).

44 Shah, D. B., Pesiridou, A., Baltuch, G. H., Malone, D. A. & O'Reardon, J. P. Functional neurosurgery in the treatment of severe obsessive compulsive disorder and major depression: overview of disease circuits and therapeutic targeting for the clinician. *Psychiatry (Edgmont)* **5**, 24-33 (2008).

45 Figee, M., Luigjes, J., Smolders, R., Valencia-Alfonso, C. E., van Wingen, G., de Kwaasteniet, B., Mantione, M., Ooms, P., de Koning, P., Vulink, N., Levar, N., Droge, L., van den Munckhof, P., Schuurman, P. R., Nederveen, A., van den Brink, W., Mazaheri, A., Vink, M. & Denys, D. Deep brain stimulation restores frontostriatal network activity in obsessive-compulsive disorder. *Nat Neurosci* **16**, 386-387, doi:10.1038/nn.3344 (2013).

46 Lipsman, N., Gerretsen, P., Torres, C., Lozano, A. M. & Giacobbe, P. A psychiatric primer for the functional neurosurgeon. *J Neurosurg Sci* **56**, 209-220 (2012).

47 Lipsman, N., Neimat, J. S. & Lozano, A. M. Deep brain stimulation for treatment-refractory obsessive-compulsive disorder: the search for a valid target. *Neurosurgery* **61**, 1-11; discussion 11-13, doi:10.1227/01.neu.0000279719.75403.f7 (2007).

48 Gros, D. F., Magruder, K. M. & Frueh, B. C. Obsessive compulsive disorder in veterans in primary care: prevalence and impairment. *Gen Hosp Psychiatry* **35**, 71-73, doi:10.1016/j.genhosppsych.2012.09.004 (2013).

49 Illumina. *Genotyping Microarray*, <http://www.illumina.com/applications/genotyping.ilmn> (2013).

50 Roach, J. C., Glusman, G., Smit, A. F., Huff, C. D., Hubley, R., Shannon, P. T., Rowen, L., Pant, K. P., Goodman, N., Bamshad, M., Shendure, J., Drmanac, R., Jorde, L. B., Hood, L. & Galas, D. J. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. *Science* **328**, 636-639, doi:10.1126/science.1186802 (2010).

51 Lupski, J. R., Reid, J. G., Gonzaga-Jauregui, C., Rio Deiros, D., Chen, D. C., Nazareth, L., Bainbridge, M., Dinh, H., Jing, C., Wheeler, D. A., McGuire, A. L., Zhang, F., Stankiewicz, P., Halperin, J. J., Yang, C., Gehman, C., Guo, D., Irikat, R. K., Tom, W., Fantin, N. J., Muzny, D. M. & Gibbs, R. A. Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. *N Engl J Med* **362**, 1181-1191, doi:10.1056/NEJMoa0908094 (2010).

52 McGuire, A. L. & Lupski, J. R. Personal genome research : what should the participant be told? *Trends Genet* **26**, 199-201, doi:10.1016/j.tig.2009.12.007 (2010).

53 Bainbridge, M. N., Wiszniewski, W., Murdock, D. R., Friedman, J., Gonzaga-Jauregui, C., Newsham, I., Reid, J. G., Fink, J. K., Morgan, M. B., Gingras, M. C., Muzny, D. M., Hoang, L. D., Yousaf, S., Lupski, J. R. & Gibbs, R. A. Whole-genome sequencing for optimized patient management. *Sci Transl Med* **3**, 87re83, doi:10.1126/scitranslmed.3002243 (2011).

54 Zumbo, P. & Mason, C. E. in *Genome Analysis: Current Procedures and Applications.* (Horizon Press. , 2014).

55 Aceview. *The AceView genes*, <http://www.ncbi.nlm.nih.gov/IEB/Research/Acembly/> (2013).

56 Lyon, G. J. *Guest post: Time to bring human genome sequencing into the clinic*, <http://www.genomesunzipped.org/2012/02/guest-post-time-to-bring-human-genome-sequencing-into-the-clinic.php> (2012).

57 Medtronic. <http://www.medtronic.com/patients/obsessive-compulsive-disorder-ocd/getting-therapy/> (2013).

58 *Individual Genome Sequencing (IGS) Test*, <http://www.illumina.com/clinical/illumina_clinical_laboratory.ilmn> (2013).

59 Lyon, G. J. & Segal, J. P. Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape. *Applied & Translational Genomics*, doi: http://dx.doi.org/10.1016/j.atg.2013.02.001, (2013).

60 Friend, S. F., Peterson, L. K., Kedl, R. M. & Dragone, L. L. SLAP deficiency increases TCR avidity leading to altered repertoire and negative selection of cognate antigen-specific CD8+ T cells. *Immunol Res* **55**, 116-124, doi:10.1007/s12026-012-8354-y (2013).

61 Omicia. <http://www.omicia.com/> (2013).

62 Zhu, M., Need, A. C., Han, Y., Ge, D., Maia, J. M., Zhu, Q., Heinzen, E. L., Cirulli, E. T., Pelak, K., He, M., Ruzzo, E. K., Gumbs, C., Singh, A., Feng, S., Shianna, K. V. & Goldstein, D. B. Using ERDS to infer copy-number variants in high-coverage genomes. *American journal of human genetics* **91**, 408-421, doi:10.1016/j.ajhg.2012.07.004 (2012).

63 Murphy, T. W., Zine, E. E. & Jenike, M. A. *Life in rewind : the story of a young courageous man who persevered over OCD and the Harvard doctor who broke all the rules to help him*. 1st edn, (William Morrow, 2009).

64 Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., Heninger, G. R. & Charney, D. S. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. *Arch Gen Psychiatry* **46**, 1006-1011 (1989).

65 Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R. & Charney, D. S. The Yale-Brown Obsessive Compulsive Scale. II. Validity. *Arch Gen Psychiatry* **46**, 1012-1016 (1989).

66 Gillihan, S. J., Williams, M. T., Malcoun, E., Yadin, E. & Foa, E. B. Common Pitfalls in Exposure and Response Prevention (EX/RP) for OCD. *J Obsessive Compuls Relat Disord* **1**, 251-257, doi:10.1016/j.jocrd.2012.05.002 (2012).

67 Greenberg, B. D., Malone, D. A., Friehs, G. M., Rezai, A. R., Kubu, C. S., Malloy, P. F., Salloway, S. P., Okun, M. S., Goodman, W. K. & Rasmussen, S. A. Three-year outcomes in deep brain stimulation for highly resistant obsessive-compulsive disorder. *Neuropsychopharmacology* **31**, 2384-2393, doi:10.1038/sj.npp.1301165 (2006).

68 Maina, G., Rosso, G., Zanardini, R., Bogetto, F., Gennarelli, M. & Bocchio-Chiavetto, L. Serum levels of brain-derived neurotrophic factor in drug-naive obsessive-compulsive patients: a case-control study. *J Affect Disord* **122**, 174-178, doi:10.1016/j.jad.2009.07.009 (2010).

69 Hall, D., Dhilla, A., Charalambous, A., Gogos, J. A. & Karayiorgou, M. Sequence Variants of the Brain-Derived Neurotrophic Factor (BDNF) Gene Are Strongly Associated with Obsessive-Compulsive Disorder. *American journal of human genetics* **73**, 370-376 (2003).

70 Rosa, A., Cuesta, M. J., Fatjó-Vilas, M., Peralta, V., Zarzuela, A. & Fañanás, L. The Val66Met polymorphism of the brain-derived neurotrophic factor gene is associated with risk for psychosis: Evidence from a family-based association study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **141B**, 135-138, doi:10.1002/ajmg.b.30266 (2006).

71 Soliman, F., Glatt, C. E., Bath, K. G., Levita, L., Jones, R. M., Pattwell, S. S., Jing, D., Tottenham, N., Amso, D., Somerville, L. H., Voss, H. U., Glover, G., Ballon, D. J., Liston, C., Teslovich, T., Van Kempen, T., Lee, F. S. & Casey, B. J. A Genetic Variant BDNF Polymorphism Alters Extinction Learning in Both Mouse and Human. *Science* **327**, 863-866, doi:10.1126/science.1181886 (2010).

72 Davis, M. The role of the amygdala in fear and anxiety. *Annu Rev Neurosci* **15**, 353-375, doi:10.1146/annurev.ne.15.030192.002033 (1992).

73 Moscarello, J. M. & LeDoux, J. E. Active avoidance learning requires prefrontal suppression of amygdala-mediated defensive reactions. *J Neurosci* **33**, 3815-3823, doi:10.1523/JNEUROSCI.2596-12.2013 (2013).

74 Rodriguez-Romaguera, J., Do Monte, F. H. & Quirk, G. J. Deep brain stimulation of the ventral striatum enhances extinction of conditioned fear. *Proc Natl Acad Sci U S A* **109**, 8764-8769, doi:10.1073/pnas.1200782109 (2012).

75 Montag, C., Reuter, M., Newport, B., Elger, C. & Weber, B. The BDNF Val66Met polymorphism affects amygdala activity in response to emotional stimuli: evidence from a genetic imaging study. *Neuroimage* **42**, 1554-1559, doi:10.1016/j.neuroimage.2008.06.008 (2008).

76 Lau, J. Y., Goldman, D., Buzas, B., Hodgkinson, C., Leibenluft, E., Nelson, E., Sankin, L., Pine, D. S. & Ernst, M. BDNF gene polymorphism (Val66Met) predicts amygdala and anterior hippocampus responses to emotional faces in anxious and depressed adolescents. *Neuroimage* **53**, 952-961, doi:10.1016/j.neuroimage.2009.11.026 (2010).

77 Allen, N. C., Bagade, S., McQueen, M. B., Ioannidis, J. P. A., Kavvoura, F. K., Khoury, M. J., Tanzi, R. E. & Bertram, L. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat Genet* **40**, 827-834, doi:http://www.nature.com/ng/journal/v40/n7/suppinfo/ng.171_S1.html (2008).

78 Frayling, T. M. Commentary: Genetic association studies see light at the end of the tunnel. *International Journal of Epidemiology* **37**, 133-135, doi:10.1093/ije/dym205 (2008).

79 Correll, C. U., Manu, P., Olshanskiy, V., Napolitano, B., Kane, J. M. & Malhotra, A. K. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *Jama* **302**, 1765-1773, doi:10.1001/jama.2009.1549 (2009).

80 van Winkel, R., Moons, T., Peerbooms, O., Rutten, B., Peuskens, J., Claes, S., van Os, J. & De Hert, M. MTHFR genotype and differential evolution of metabolic parameters after initiation of a second generation antipsychotic: an observational study. *Int Clin Psychopharmacol* **25**, 270-276, doi:10.1097/YIC.0b013e32833bc60d (2010).

81 Mancama, D., Mata, I., Kerwin, R. W. & Arranz, M. J. Choline acetyltransferase variants and their influence in schizophrenia and olanzapine response. *Am J Med Genet B Neuropsychiatr Genet* **144B**, 849-853, doi:10.1002/ajmg.b.30468 (2007).

82 Collip, D., van Winkel, R., Peerbooms, O., Lataster, T., Thewissen, V., Lardinois, M., Drukker, M., Rutten, B. P., Van Os, J. & Myin-Germeys, I. COMT Val158Met-stress interaction in psychosis: role of background psychosis risk. *CNS Neurosci Ther* **17**, 612-619, doi:10.1111/j.1755-5949.2010.00213.x (2011).

83 Dumontheil, I., Roggeman, C., Ziermans, T., Peyrard-Janvid, M., Matsson, H., Kere, J. & Klingberg, T. Influence of the COMT genotype on

working memory and brain activity changes during development. *Biol Psychiatry* **70**, 222-229, doi:10.1016/j.biopsych.2011.02.027 (2011).
84 Lajin, B., Alachkar, A., Hamzeh, A. R., Michati, R. & Alhaj, H. No association between Val158Met of the COMT gene and susceptibility to schizophrenia in the Syrian population. *N Am J Med Sci* **3**, 176-178, doi:10.4297/najms.2011.3176 (2011).
85 Raznahan, A., Greenstein, D., Lee, Y., Long, R., Clasen, L., Gochman, P., Addington, A., Giedd, J. N., Rapoport, J. L. & Gogtay, N. Catechol-o-methyl transferase (COMT) val158met polymorphism and adolescent cortical development in patients with childhood-onset schizophrenia, their non-psychotic siblings, and healthy controls. *Neuroimage* **57**, 1517-1523, doi:10.1016/j.neuroimage.2011.05.032 (2011).
86 Lopez-Garcia, P., Young Espinoza, L., Molero Santos, P., Marin, J. & Ortuno Sanchez-Pedreno, F. Impact of COMT genotype on cognition in schizophrenia spectrum patients and their relatives. *Psychiatry Res*, doi:10.1016/j.psychres.2012.09.043 (2012).
87 Singh, J. P., Volavka, J., Czobor, P. & Van Dorn, R. A. A meta-analysis of the Val158Met COMT polymorphism and violent behavior in schizophrenia. *PLoS One* **7**, e43423, doi:10.1371/journal.pone.0043423 (2012).
88 Ira, E., Zanoni, M., Ruggeri, M., Dazzan, P. & Tosato, S. COMT, neuropsychological function and brain structure in schizophrenia: a systematic review and neurobiological interpretation. *J Psychiatry Neurosci* **38**, 120178, doi:10.1503/jpn.120178 (2013).
89 Roffman, J. L., Gollub, R. L., Calhoun, V. D., Wassink, T. H., Weiss, A. P., Ho, B. C., White, T., Clark, V. P., Fries, J., Andreasen, N. C., Goff, D. C. & Manoach, D. S. MTHFR 677C --> T genotype disrupts prefrontal function in schizophrenia through an interaction with COMT 158Val --> Met. *Proc Natl Acad Sci U S A* **105**, 17573-17578, doi:10.1073/pnas.0803727105 (2008).
90 Alonso, P., Lopez-Sola, C., Gratacos, M., Fullana, M. A., Segalas, C., Real, E., Cardoner, N., Soriano-Mas, C., Harrison, B. J., Estivill, X. & Menchon, J. M. The interaction between Comt and Bdnf variants influences obsessive-compulsive-related dysfunctional beliefs. *J Anxiety Disord* **27**, 321-327, doi:10.1016/j.janxdis.2013.02.012 (2013).
91 Lundblad, M. S., Stark, K., Eliasson, E., Oliw, E. & Rane, A. Biosynthesis of epoxyeicosatrienoic acids varies between polymorphic CYP2C enzymes. *Biochem Biophys Res Commun* **327**, 1052-1057, doi:10.1016/j.bbrc.2004.12.116 (2005).
92 Sim, S. C. & Ingelman-Sundberg, M. Update on allele nomenclature for human cytochromes P450 and the Human Cytochrome P450 Allele (CYP-allele) Nomenclature Database. *Methods Mol Biol* **987**, 251-259, doi:10.1007/978-1-62703-321-3_21 (2013).
93 Nelson, D. R., Zeldin, D. C., Hoffman, S. M., Maltais, L. J., Wain, H. M. & Nebert, D. W. Comparison of cytochrome P450 (CYP) genes from the mouse and human genomes, including nomenclature recommendations for genes, pseudogenes and alternative-splice variants. *Pharmacogenetics and Genomics* **14**, 1-18 (2004).
94 Pigott, T. A. & Seay, S. M. A review of the efficacy of selective serotonin reuptake inhibitors in obsessive-compulsive disorder. *J Clin Psychiatry* **60**, 101-106 (1999).
95 Pigott, T. A., Pato, M. T., Bernstein, S. E., Grover, G. N., Hill, J. L., Tolliver, T. J. & Murphy, D. L. Controlled comparisons of clomipramine and fluoxetine in the treatment of obsessive-compulsive disorder. Behavioral and biological results. *Arch Gen Psychiatry* **47**, 926-932 (1990).
96 Ring, B. J., Eckstein, J. A., Gillespie, J. S., Binkley, S. N., VandenBranden, M. & Wrighton, S. A. Identification of the human cytochromes p450 responsible for in vitro formation of R- and S-norfluoxetine. *J Pharmacol Exp Ther* **297**, 1044-1050 (2001).
97 Zhou, S. F., Liu, J. P. & Chowbay, B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. *Drug Metab Rev* **41**, 89-295, doi:10.1080/03602530902843483 (2009).
98 Johnson, M. R., Wang, K., Tillmanns, S., Albin, N. & Diasio, R. B. Structural Organization of the Human Dihydropyrimidine Dehydrogenase Gene. *Cancer Research* **57**, 1660-1663 (1997).
99 Shestopal, S. A., Johnson, M. R. & Diasio, R. B. Molecular cloning and characterization of the human dihydropyrimidine dehydrogenase promoter. *Biochimica et Biophysica Acta (BBA) - Gene Structure and Expression* **1494**, 162-169, doi:http://dx.doi.org/10.1016/S0167-4781(00)00213-X (2000).
100 ACMG. (2013).
101 Reese, M. G., Moore, B., Batchelor, C., Salas, F., Cunningham, F., Marth, G. T., Stein, L., Flicek, P., Yandell, M. & Eilbeck, K. A standard variation file format for human genome sequences. *Genome Biol* **11**, R88, doi:10.1186/gb-2010-11-8-r88 (2010).
102 Eilbeck, K. *GVFclin*, <http://www.sequenceontology.org/resources/gvfclin.html> (2013).
103 Conn, J. VA to update VistA EHR. *Mod Healthc* **41**, 17 (2011).
104 Protti, D. & Groen, P. Implementation of the Veterans Health Administration VistA clinical information system around the world. *Healthc Q* **11**, 83-89 (2008).
105 Kuzmak, P. M. & Dayhoff, R. E. The Department of Veterans Affairs integration of imaging into the healthcare enterprise using the VistA Hospital Information System and Digital Imaging and Communications in Medicine. *J Digit Imaging* **11**, 53-64 (1998).
106 Brown, S. H., Lincoln, M. J., Groen, P. J. & Kolodner, R. M. VistA--U.S. Department of Veterans Affairs national-scale HIS. *Int J Med Inform* **69**, 135-156 (2003).
107 Fins, J. J., Dorfman, G. S. & Pancrazio, J. J. Challenges to deep brain stimulation: a pragmatic response to ethical, fiscal, and regulatory concerns. *Ann N Y Acad Sci* **1265**, 80-90, doi:10.1111/j.1749-6632.2012.06598.x (2012).
108 Synofzik, M., Fins, J. J. & Schlaepfer, T. E. A neuromodulation experience registry for deep brain stimulation studies in psychiatric research: rationale and recommendations for implementation. *Brain Stimul* **5**, 653-655, doi:10.1016/j.brs.2011.10.003 (2012).
109 Fins, J. J., Schlaepfer, T. E., Nuttin, B., Kubu, C. S., Galert, T., Sturm, V., Merkel, R. & Mayberg, H. S. Ethical guidance for the management of conflicts of interest for researchers, engineers and clinicians engaged in the development of therapeutic deep brain stimulation. *J Neural Eng* **8**, 033001, doi:10.1088/1741-2560/8/3/033001 (2011).
110 Fins, J. J., Mayberg, H. S., Nuttin, B., Kubu, C. S., Galert, T., Sturm, V., Stoppenbrink, K., Merkel, R. & Schlaepfer, T. E. Misuse of the FDA's humanitarian device exemption in deep brain stimulation for obsessive-compulsive disorder. *Health Aff (Millwood)* **30**, 302-311, doi:10.1377/hlthaff.2010.0157 (2011).
111 Fins, J. J. & Schiff, N. D. Conflicts of interest in deep brain stimulation research and the ethics of transparency. *J Clin Ethics* **21**, 125-132 (2010).
112 Fins, J. J. Deep Brain Stimulation, Free Markets and the Scientific Commons: Is It time to Revisit the Bayh-Dole Act of 1980? *Neuromodulation* **13**, 153-159, doi:10.1111/j.1525-1403.2009.00238.x (2010).
113 Erickson-Davis, C. Ethical concerns regarding commercialization of deep brain stimulation for obsessive compulsive disorder. *Bioethics* **26**, 440-446, doi:10.1111/j.1467-8519.2011.01886.x (2012).
114 Kim, T. I., McCall, J. G., Jung, Y. H., Huang, X., Siuda, E. R., Li, Y., Song, J., Song, Y. M., Pao, H. A., Kim, R. H., Lu, C., Lee, S. D., Song, I. S., Shin, G., Al-Hasani, R., Kim, S., Tan, M. P., Huang, Y., Omenetto, F. G., Rogers, J. A. & Bruchas, M. R. Injectable, cellular-scale optoelectronics with applications for wireless optogenetics. *Science* **340**, 211-216, doi:10.1126/science.1232437 (2013).
115 Alivisatos, A. P., Andrews, A. M., Boyden, E. S., Chun, M., Church, G. M., Deisseroth, K., Donoghue, J. P., Fraser, S. E., Lippincott-Schwartz, J., Looger, L. L., Masmanidis, S., McEuen, P. L., Nurmikko, A. V., Park, H., Peterka, D. S., Reid, C., Roukes, M. L., Scherer, A., Schnitzer, M., Sejnowski, T. J., Shepard, K. L., Tsao, D., Turrigiano, G., Weiss, P. S., Xu, C., Yuste, R. & Zhuang, X. Nanotools for neuroscience and brain activity mapping. *ACS Nano* **7**, 1850-1866, doi:10.1021/nn4012847 (2013).
116 Alivisatos, A. P., Chun, M., Church, G. M., Deisseroth, K., Donoghue, J. P., Greenspan, R. J., McEuen, P. L., Roukes, M. L., Sejnowski, T. J.,

Weiss, P. S. & Yuste, R. Neuroscience. The brain activity map. *Science* **339**, 1284-1285, doi:10.1126/science.1236939 (2013).
117 Pais-Vieira, M., Lebedev, M., Kunicki, C., Wang, J. & Nicolelis, M. A. A brain-to-brain interface for real-time sharing of sensorimotor information. *Sci Rep* **3**, 1319, doi:10.1038/srep01319 (2013).
118 Thomson, E. E., Carra, R. & Nicolelis, M. A. Perceiving invisible light through a somatosensory cortical prosthesis. *Nat Commun* **4**, 1482, doi:10.1038/ncomms2497 (2013).
119 Nicolelis, M. A. Mind in motion. *Sci Am* **307**, 58-63 (2012).
120 Moreno-De-Luca, A., Myers, S. M., Challman, T. D., Moreno-De-Luca, D., Evans, D. W. & Ledbetter, D. H. Developmental brain dysfunction: revival and expansion of old concepts based on new genetic evidence. *The Lancet Neurology* **12**, 406-414 (2013).
121 Nielsen, R., Paul, J. S., Albrechtsen, A. & Song, Y. S. Genotype and SNP calling from next-generation sequencing data. *Nat Rev Genet* **12**, 443-451, doi:10.1038/nrg2986 (2011).
122 O'Rawe, J., Jiang, T., Sun, G., Wu, Y., Wang, W., Hu, J., Bodily, P., Tian, L., Hakonarson, H., Johnson, W. E., Wei, Z., Wang, K. & Lyon, G. J. Low concordance of multiple variant-calling pipelines: practical implications for exome and genome sequencing. *Genome Med* **5**, 28, doi:10.1186/gm432 (2013).
123 Klei, L., Sanders, S. J., Murtha, M. T., Hus, V., Lowe, J. K., Willsey, A. J., Moreno-De-Luca, D., Yu, T. W., Fombonne, E., Geschwind, D., Grice, D. E., Ledbetter, D. H., Lord, C., Mane, S. M., Lese Martin, C., Martin, D. M., Morrow, E. M., Walsh, C. A., Melhem, N. M., Chaste, P., Sutcliffe, J. S., State, M. W., Cook, E. H., Jr., Roeder, K. & Devlin, B. Common genetic variants, acting additively, are a major source of risk for autism. *Mol Autism* **3**, 9, doi:10.1186/2040-2392-3-9 (2012).
124 Mitchell, K. J. & Porteous, D. J. Rethinking the genetic architecture of schizophrenia. *Psychol Med* **41**, 19-32, doi:10.1017/S003329171000070X (2011).
125 Mitchell, K. J. What is complex about complex disorders? *Genome Biol* **13**, 237, doi:10.1186/gb-2012-13-1-237 (2012).
126 Visscher, P. M., Goddard, M. E., Derks, E. M. & Wray, N. R. Evidence-based psychiatric genetics, AKA the false dichotomy between common and rare variant hypotheses. *Mol Psychiatry*, doi:10.1038/mp.2011.65 (2011).
127 Kajiwara, K., Berson, E. & Dryja, T. Digenic retinitis pigmentosa due to mutations at the unlinked peripherin/RDS and ROM1 loci. *Science* **264**, 1604-1608, doi:10.1126/science.8202715 (1994).
128 Katsanis, N., Ansley, S. J., Badano, J. L., Eichers, E. R., Lewis, R. A., Hoskins, B. E., Scambler, P. J., Davidson, W. S., Beales, P. L. & Lupski, J. R. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. *Science* **293**, 2256-2259, doi:10.1126/science.1063525 (2001).
129 El-Hattab, A. W., Zhang, F., Maxim, R., Christensen, K. M., Ward, J. C., Hines-Dowell, S., Scaglia, F., Lupski, J. R. & Cheung, S. W. Deletion and duplication of 15q24: Molecular mechanisms and potential modification by additional copy number variants. *Genet Med* **12**, 573-586 (2010).
130 Davis, E. E., Zhang, Q., Liu, Q., Diplas, B. H., Davey, L. M., Hartley, J., Stoetzel, C., Szymanska, K., Ramaswami, G., Logan, C. V., Muzny, D. M., Young, A. C., Wheeler, D. A., Cruz, P., Morgan, M., Lewis, L. R., Cherukuri, P., Maskeri, B., Hansen, N. F., Mullikin, J. C., Blakesley, R. W., Bouffard, G. G., Gyapay, G., Rieger, S., Tonshoff, B., Kern, I., Soliman, N. A., Neuhaus, T. J., Swoboda, K. J., Kayserili, H., Gallagher, T. E., Lewis, R. A., Bergmann, C., Otto, E. A., Saunier, S., Scambler, P. J., Beales, P. L., Gleeson, J. G., Maher, E. R., Attie-Bitach, T., Dollfus, H., Johnson, C. A., Green, E. D., Gibbs, R. A., Hildebrandt, F., Pierce, E. A. & Katsanis, N. TTC21B contributes both causal and modifying alleles across the ciliopathy spectrum. *Nat Genet*, doi:ng.756 [pii]
10.1038/ng.756 (2011).
131 Lemmers, R. J. L. F., Tawil, R., Petek, L. M., Balog, J., Block, G. J., Santen, G. W. E., Amell, A. M., van der Vliet, P. J., Almomani, R., Straasheijm, K. R., Krom, Y. D., Klooster, R., Sun, Y., den Dunnen, J. T., Helmer, Q., Donlin-Smith, C. M., Padberg, G. W., van Engelen, B. G. M., de Greef, J. C., Aartsma-Rus, A. M., Frants, R. R., de Visser, M., Desnuelle, C., Sacconi, S., Filippova, G. N., Bakker, B., Bamshad, M. J., Tapscott, S. J., Miller, D. G. & van der Maarel, S. M. Digenic inheritance of an SMCHD1 mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2. *Nat Genet* **44**, 1370-1374, doi:http://www.nature.com/ng/journal/v44/n12/abs/ng.2454.html - supplementary-information (2012).
132 Lai, J., Li, R., Xu, X., Jin, W., Xu, M., Zhao, H., Xiang, Z., Song, W., Ying, K., Zhang, M., Jiao, Y., Ni, P., Zhang, J., Li, D., Guo, X., Ye, K., Jian, M., Wang, B., Zheng, H., Liang, H., Zhang, X., Wang, S., Chen, S., Li, J., Fu, Y., Springer, N. M., Yang, H., Wang, J., Dai, J., Schnable, P. S. & Wang, J. Genome-wide patterns of genetic variation among elite maize inbred lines. *Nat Genet* **42**, 1027-1030, doi:http://www.nature.com/ng/journal/v42/n11/abs/ng.684.html - supplementary-information (2010).
133 Bloom, J. S., Ehrenreich, I. M., Loo, W. T., Lite, T. L. & Kruglyak, L. Finding the sources of missing heritability in a yeast cross. *Nature* **494**, 234-237, doi:10.1038/nature11867 (2013).
134 Zuk, O., Hechter, E., Sunyaev, S. R. & Lander, E. S. The mystery of missing heritability: Genetic interactions create phantom heritability. *Proc Natl Acad Sci U S A* **109**, 1193-1198, doi:10.1073/pnas.1119675109 (2012).
135 Keller, E. F. *The mirage of a space between nature and nurture*. (Duke University Press, 2010).
136 Casanueva, M. O., Burga, A. & Lehner, B. Fitness trade-offs and environmentally induced mutation buffering in isogenic C. elegans. *Science* **335**, 82-85, doi:10.1126/science.1213491 (2012).
137 Dolinoy, D. C., Weidman, J. R., Waterland, R. A. & Jirtle, R. L. Maternal genistein alters coat color and protects Avy mouse offspring from obesity by modifying the fetal epigenome. *Environ Health Perspect* **114**, 567-572 (2006).
138 Bernal, A. J. & Jirtle, R. L. Epigenomic disruption: the effects of early developmental exposures. *Birth Defects Res A Clin Mol Teratol* **88**, 938-944, doi:10.1002/bdra.20685 (2010).
139 Weinhouse, C., Anderson, O. S., Jones, T. R., Kim, J., Liberman, S. A., Nahar, M. S., Rozek, L. S., Jirtle, R. L. & Dolinoy, D. C. An expression microarray approach for the identification of metastable epialleles in the mouse genome. *Epigenetics* **6**, 1105-1113, doi:10.4161/epi.6.9.17103 (2011).
140 Holmes, F. L. & Summers, W. C. *Reconceiving the gene : Seymour Benzer's adventures in phage genetics*. (Yale University Press, 2006).
141 Greenspan, R. J. Biological indeterminacy. *Sci Eng Ethics* **18**, 447-452, doi:10.1007/s11948-012-9379-2 (2012).
142 Greenspan, R. J. Selection, gene interaction, and flexible gene networks. *Cold Spring Harb Symp Quant Biol* **74**, 131-138, doi:10.1101/sqb.2009.74.029 (2009).
143 Greenspan, R. J. Seymour Benzer (1921-2007). *Curr Biol* **18**, R106-110 (2008).
144 Kendler, K. S. & Greenspan, R. J. The nature of genetic influences on behavior: lessons from "simpler" organisms. *The American journal of psychiatry* **163**, 1683-1694, doi:10.1176/appi.ajp.163.10.1683 (2006).
145 van Swinderen, B. & Greenspan, R. J. Flexibility in a gene network affecting a simple behavior in Drosophila melanogaster. *Genetics* **169**, 2151-2163, doi:10.1534/genetics.104.032631 (2005).
146 Blount, Z. D., Barrick, J. E., Davidson, C. J. & Lenski, R. E. Genomic analysis of a key innovation in an experimental Escherichia coli population. *Nature* **489**, 513-518, doi:10.1038/nature11514 (2012).
147 Meyer, J. R., Dobias, D. T., Weitz, J. S., Barrick, J. E., Quick, R. T. & Lenski, R. E. Repeatability and contingency in the evolution of a key

innovation in phage lambda. *Science* **335**, 428-432, doi:10.1126/science.1214449 (2012).
148 Biesecker, B. B. & Peay, H. L. Genomic sequencing for psychiatric disorders: promise and challenge. *Int J Neuropsychopharmacol*, 1-6, doi:10.1017/S146114571300014X (2013).
149 ACMG. (2013).
150 Yu, J. H., Jamal, S. M., Tabor, H. K. & Bamshad, M. J. Self-guided management of exome and whole-genome sequencing results: changing the results return model. *Genet Med*, doi:10.1038/gim.2013.35 (2013).
151 *Support the Proposed Federal Rule to Expand the Rights of Patients to Access Their Test Results*, <http://strataconf.com/rx2012/public/content/consensus> (2013).
152 Lyon, G. J. Personalized medicine: Bring clinical standards to human-genetics research. *Nature* **482**, 300-301, doi:10.1038/482300a (2012).
153 Kaufman, D., Bollinger, J., Dvoskin, R. & Scott, J. Preferences for opt-in and opt-out enrollment and consent models in biobank research: a national survey of Veterans Administration patients. *Genetics in medicine : official journal of the American College of Medical Genetics* **14**, 787-794, doi:10.1038/gim.2012.45 (2012).
154 Cannon-Albright, L. A., Dintelman, S., Maness, T., Backus, S., Thomas, A. & Meyer, L. J. Creation of a national resource with linked genealogy and phenotypic data: the Veterans Genealogy Project. *Genetics in medicine : official journal of the American College of Medical Genetics*, doi:10.1038/gim.2012.171 (2013).
155 Sacks, O. W. *An anthropologist on Mars : seven paradoxical tales*. 1st edn, (Alfrd A. Knopf, 1995).
156 Sacks, O. W. *The man who mistook his wife for a hat and other clinical tales*. 1st Touchstone edn, (Simon & Schuster, 1998).
157 Luria, A. R. *The man with a shattered world; the history of a brain wound*. (Basic Books, 1972).
158 Luria, A. R. *The mind of a mnemonist : a little book about a vast memory*. (H. Regnery, 1976).
159 Van Horn, J. D., Irimia, A., Torgerson, C. M., Chambers, M. C., Kikinis, R. & Toga, A. W. Mapping connectivity damage in the case of Phineas Gage. *PLoS One* **7**, e37454, doi:10.1371/journal.pone.0037454 (2012).
160 Ratiu, P., Talos, I. F., Haker, S., Lieberman, D. & Everett, P. The tale of Phineas Gage, digitally remastered. *J Neurotrauma* **21**, 637-643, doi:10.1089/089771504774129964 (2004).
161 Eichenbaum, H. What H.M. taught us. *J Cogn Neurosci* **25**, 14-21, doi:10.1162/jocn_a_00285 (2013).
162 Worthey, E. A., Mayer, A. N., Syverson, G. D., Helbling, D., Bonacci, B. B., Decker, B., Serpe, J. M., Dasu, T., Tschannen, M. R., Veith, R. L., Basehore, M. J., Broeckel, U., Tomita-Mitchell, A., Arca, M. J., Casper, J. T., Margolis, D. A., Bick, D. P., Hessner, M. J., Routes, J. M., Verbsky, J. W., Jacob, H. J. & Dimmock, D. P. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genetics in medicine : official journal of the American College of Medical Genetics* **13**, 255-262, doi:10.1097/GIM.0b013e3182088158 (2011).
163 Sporn, M. B. Perspective: The big C - for Chemoprevention. *Nature* **471**, S10-11, doi:10.1038/471S10a (2011).
164 Patel, C., Sivadas, A., Tabassum, R., Preeprem, T., Zhao, J., Arafat, D., Chen, R., Morgan, A., Martin, G., Brigham, K., Butte, A. & Gibson, G. Whole Genome Sequencing in support of Wellness and Health Maintenance. *Genome Medicine* **5**, 58 (2013).
165 Ashley, E. A., Butte, A. J., Wheeler, M. T., Chen, R., Klein, T. E., Dewey, F. E., Dudley, J. T., Ormond, K. E., Pavlovic, A., Morgan, A. A., Pushkarev, D., Neff, N. F., Hudgins, L., Gong, L., Hodges, L. M., Berlin, D. S., Thorn, C. F., Sangkuhl, K., Hebert, J. M., Woon, M., Sagreiya, H., Whaley, R., Knowles, J. W., Chou, M. F., Thakuria, J. V., Rosenbaum, A. M., Zaranek, A. W., Church, G. M., Greely, H. T., Quake, S. R. & Altman, R. B. Clinical assessment incorporating a personal genome. *Lancet* **375**, 1525-1535, doi:10.1016/s0140-6736(10)60452-7 (2010).
166 Jacob, H. J., Abrams, K., Bick, D. P., Brodie, K., Dimmock, D. P., Farrell, M., Geurts, J., Harris, J., Helbling, D., Joers, B. J., Kliegman, R., Kowalski, G., Lazar, J., Margolis, D. A., North, P., Northup, J., Roquemore-Goins, A., Scharer, G., Shimoyama, M., Strong, K., Taylor, B., Tsaih, S.-W., Tschannen, M. R., Veith, R. L., Wendt-Andrae, J., Wilk, B. & Worthey, E. A. Genomics in Clinical Practice: Lessons from the Front Lines. *Sci Transl Med* **5**, 194cm195, doi:10.1126/scitranslmed.3006468 (2013).

Figure 1

Sagittal and transverse computed tomography (CT) images of the brain and skull of M.A.

We show here sagittal and transverse sections taken from CT scans. Imaging was performed before (**A**) and after (**B**) M.A. received deep brain stimulation surgery for his treatment refractory OCD. Two deep brain stimulator probes can be seen to be in place from a bifrontal approach (**B**), with tips of the probes located in the region of the hypothalamus. Leads traverse through the left scalp soft tissues. Streak artifact from the leads somewhat obscures visualization of the adjacent bifrontal and left parietal parenchyma. We did not observe any intracranial hemorrhage, mass effect or midline shift or extra-axial fluid collection. Brain parenchyma was normal in volume and contour.

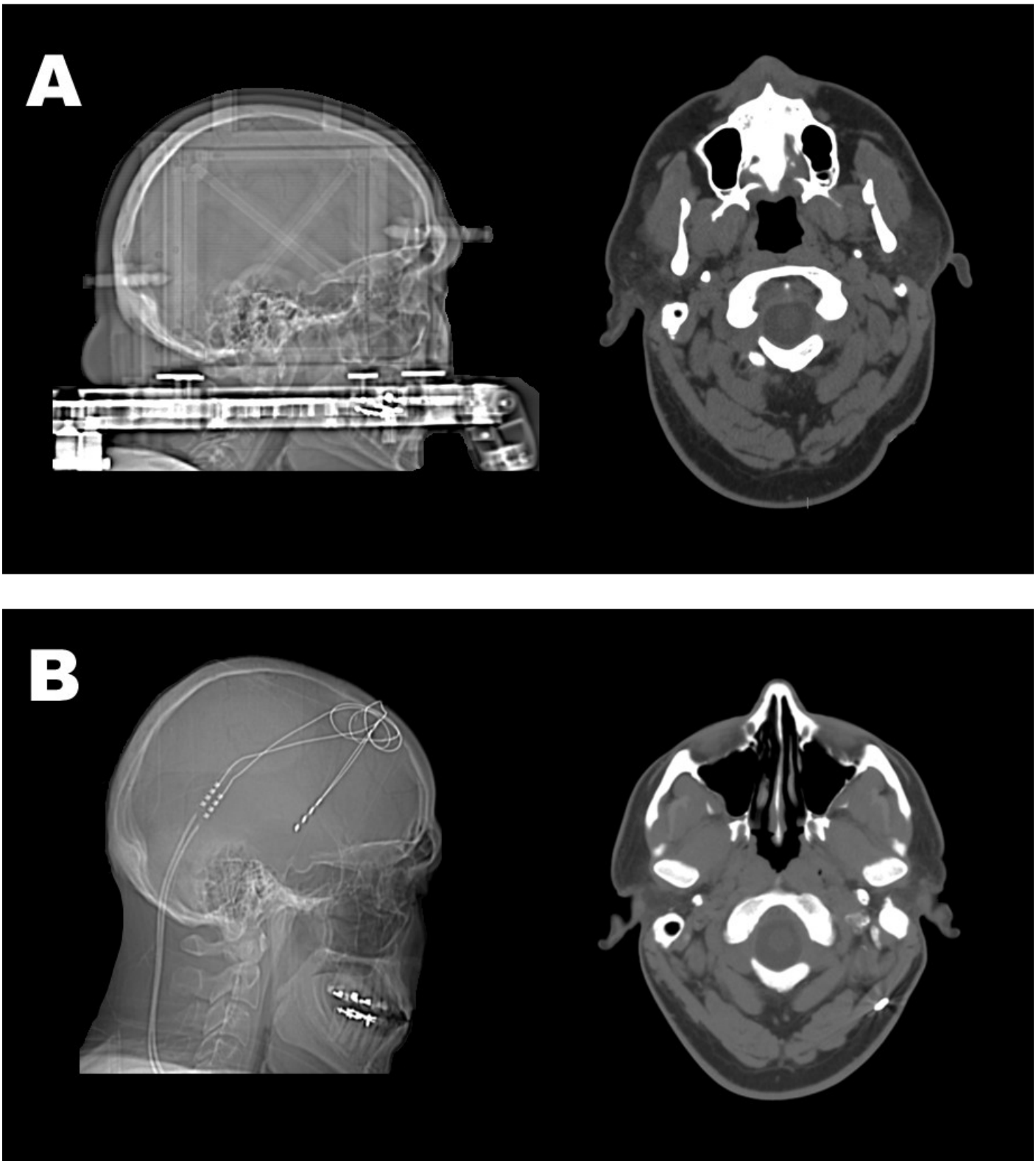

Figure 2

Implementation of the analytic-interpretive split model for the clinical incorporation of a whole genome.

We have implemented the analytic-interpretive split model here with M.A., with WGS being performed in a CLIA certified and CAP accredited lab at Illumina as part of the Individual Genome Sequencing test developed by them. The WGS acts as a discrete deliverable clinical unit from which multiple downstream interpretive analyses were performed. We used the ERDS CNV caller, the Golden Helix SVS CNAM for CNV calling, and the Omicial Opal and the AssureRx Health Inc. pipelines for variant annotation and clinical interpretation of genomic variants. By archiving and offering to him the encrypted hard drive containing his "raw" sequencing data, any number of people, including the individual and/or his/her health care providers can analyze his genome for years to come. Abbreviations are as follows: CLIA, Clinical Laboratory Improvement Amendments; CAP, College of American Pathologists; CASAVA, Consensus Assessment of Sequence and Variation; ERDS, Estimation by Read Depth with SNVs; CNAM, Copy Number Analysis Method; WGS, Whole Genome Sequencing.

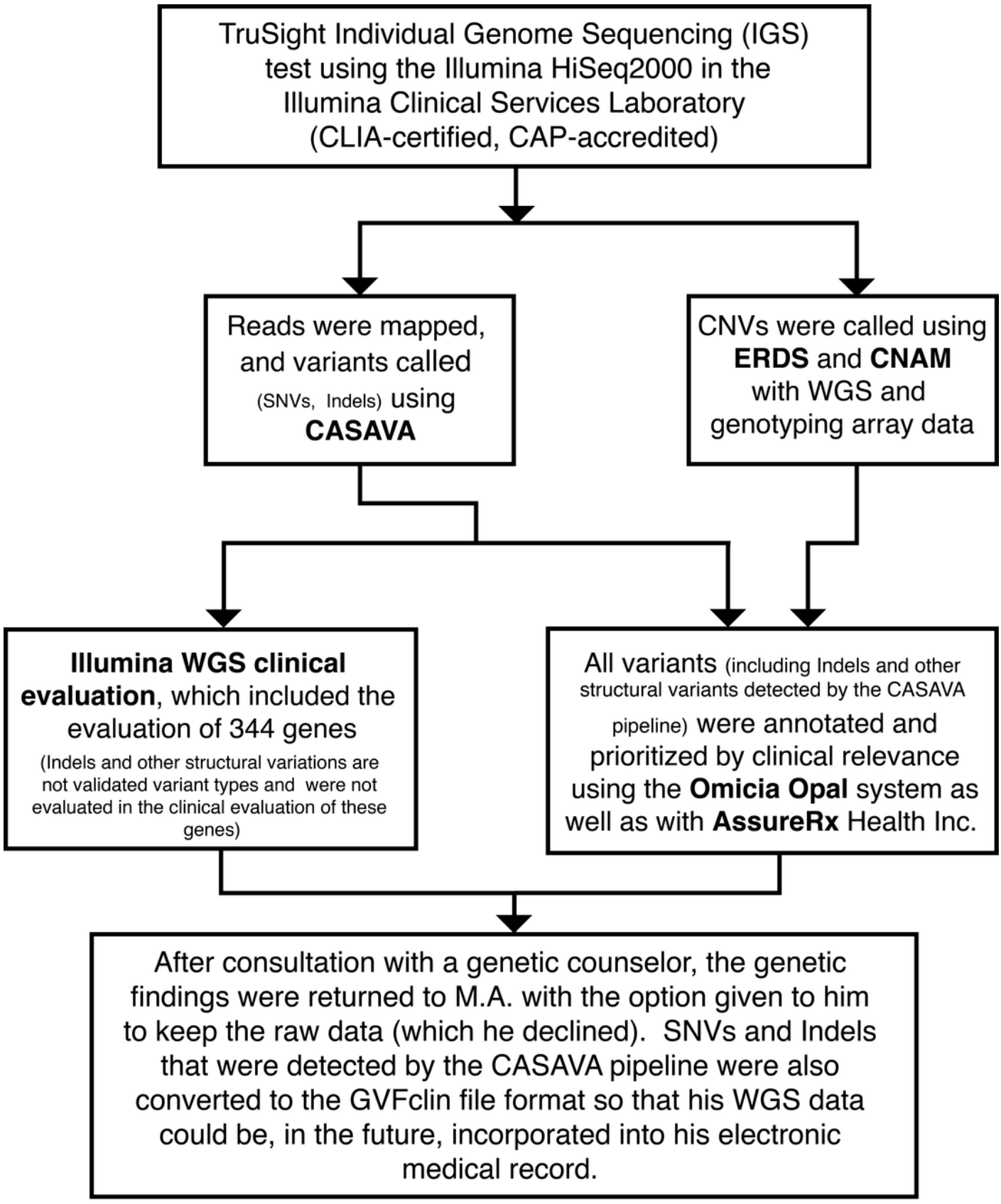

Figure 3

Yale Brown Obsessive Compulsive Scale (YBOCS) scores were measured for M.Aover a three year and seven months period of time.

A time series plot (**A**) shows a steady decline in YBOCS scores over the period of time spanning his DBS surgery (**s**) and treatment. Incremental adjustments to neurostimulator voltage are plotted over a period of time following DBS surgery. Mean YBOCS scores are plotted for sets of measurements taken before and after Deep Brain Stimulation (DBS) surgery (**B**). A one-tailed unpaired t test with Welch's correction results in a p value of 0.0056,demonstrating a significant differencebetween YBOCS scores measured before and after the time of surgery.

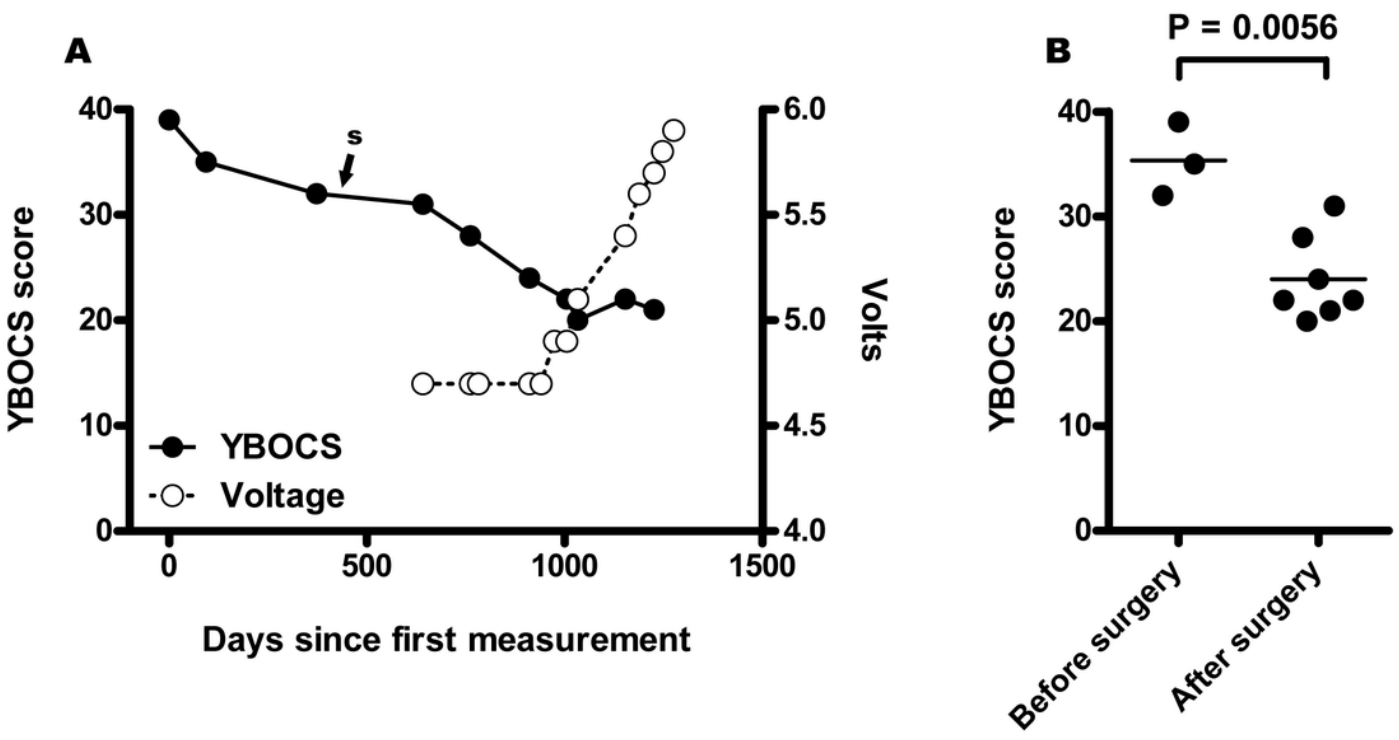

Table 1 (on next page)

A summary of three clinically relevant alleles found in the sequencing results of M.A.

Variations in *MTHFR*, *BDNF*, and *ChAT* were found to be of potential clinical relevance for this person, as they are all implicated in contributing to the susceptibility and development of many neuropsychiatric disorders that resemble those present within M.A. A brief summary of the characteristics of each variation is shown, including the gene name, genomic coordinates, amino acid change, zygosity, variation type, estimated population frequency and putative clinical significance.

Gene name	Genomic coordinates	Amino acid change	Zygosity	Variation type	Population Frequency	Clinical significance
MTHFR	chr1: 11854476	Glu>Ala	heterozygous	non-synon	T:77% G:23%	Susceptibility to psychoses, schizophrenia occlusive vascular disease, neural tube defects, colon cancer, acute leukemia, and methylenetetra-hydrofolate reductase def-iciency
BDNF	chr11: 27679916	Val>Met	heterozygous	non-synon	C:77% T:23%	Susceptibility to OCD, psychosis, and diminished response to exposure therapy
CHAT	chr10: 50824117	Asp>Asn	heterozygous	non-synon	G:85% A:15%	Susceptibility to schizophrenia and other psychopathological disorders.