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Psychiatric molecular genetics and the ethics of social promises

John Z. Sadler, MD and Daniel W. Foster, M.D.[Professor of Medical Ethics, Professor of Psychiatry & Clinical Sciences]

Departments of Psychiatry & Clinical Sciences, Program in Ethics in Science & Medicine, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9070

John Z. Sadler: John.Sadler@UTSouthwestern.edu

Abstract

A recent literature review of commentaries and ‘state of the art’ articles from researchers in psychiatric genetics (PMG) offers a consensus about progress in the science of genetics, disappointments in the discovery of new and effective treatments, and a general optimism about the future of the field. I argue that optimism for the field of psychiatric molecular genetics (PMG) is overwrought, and consider progress in the field in reference to a sample estimate of US National Institute of Mental Health funding for this paradigm for the years 2008 and 2009. I conclude that the amounts of financial investment in PMG is questionable from an ethical perspective, given other research and clinical needs in the USA.

Keywords

psychiatry; mental disorders; molecular genetics; ethics

The thesis for this paper is relatively easy to state, but defending the thesis is more difficult, requiring more indirect argument and indirect evidence than I am typically comfortable with. I think the best I can do for the purpose of this article for JBI is simply raise an issue. Nevertheless, the principle emerging from the discussion I think is important, and perhaps others can handle much better what for me has been an unraised and unanswered question of ethical significance. A direct assessment of the relative successes and failures of the psychiatric genetics paradigm would warrant a book-length treatment, well beyond the potential of a single journal article.

The thesis is this: At least for the United States, the promise of molecular genetics in psychiatry has been overwrought, leading to a skewed funding allocation for research in the field. The time has come, and is perhaps overdue, to consider the reduction of research grant investment in this area and, in a principled way, rethink and rearrange research funding priorities that do not require decades of development in order to make a clinical impact. I should qualify such a thesis right away. I am not suggesting that funding for psychiatric molecular genetics (PMG) should stop and thereby bring all PMG research to a screeching halt. I want to claim instead that the PMG share here may not be justified ethically and needs reassessment. I write from a United States perspective not out of provincial narcissism, but from a practical standpoint – the US research funding context is the one I am familiar with. That I’m choosing to submit this to a journal on the other side of the world from the US is probably no mistake either, in that what follows stands to at best annoy people working in the PMG field!

The paper proceeds by first considering how successful the psychiatric molecular genetics *modus operandi* has been in generating breakthroughs in the treatment, of people with

mental disorders, according to the investigators themselves. This approach is not intended as a typical “appeal to authority” type rhetorical argument, but rather to address the viewpoints of stakeholders who stand to benefit from an ongoing generous PMG grant support. The second stage of the paper describes the difficulties in capturing attempts to estimate the amounts of money spent on this research endeavor, requiring some description of the US National Institute of Mental Health (NIMH)’s structure and grantmaking procedures. This material is important to make a credible case for what follows, which is a claim about a very large amount of money spent on a particular theoretical approach to psychiatric etiology. A third stage of the paper provides some indications of the funding amounts involved, requiring an acknowledgment of limitations. A fourth stage considers the ethical issues in continuing large amounts of funding for PMG instead of other social and clinical needs of the mental health field. Concluding comments situate these ethical issues in the context of the history of psychiatry and public funding/support, and the limitations of the “magic bullet” metaphor in psychiatry and especially psychiatric molecular genetics.

What kind of progress in PMG?

Kendler (2005a) makes an important set of distinctions when considering the psychiatric genetics field as a whole. He distinguishes four “paradigms” in the field: (1) basic genetic epidemiology (2) advanced genetic epidemiology (3) gene finding and (4) molecular genetics. Genetic and advanced genetic epidemiology intend to discover individual differences in risk (liability) due to genetic rather than familial or environmental factors. Advanced genetic epidemiology intends to clarify relationships between genetic and environmental risk for disorders, using finer-grained concepts like shared/nonshared environment, staging and disease development, etc. Gene finding is intended to find particular gene/genes (locus./loci) that have differential impact on the development of mental disorders. It does so by comparing statistical risks for alleles (gene structural variations) in sample populations, or studies larger DNA “chunks” where allelic variation occurs (haplotypes). The fourth paradigm, molecular genetics, concerns itself with biological mechanisms of disease at the molecular level, implicated by genes suspected or implicated in the disorder by gene finding. Simply put, molecular genetics links gene function to molecular and cellular etiological mechanisms for disorders. For the purposes of this article, I will not be discussing basic or advanced genetic epidemiology, and lump gene finding and molecular genetics in Kendler’s sense together as “PMG.” For my purposes here, the molecular genetic paradigm described by Kendler is dependent upon the gene finding paradigm in order to elucidate mechanisms of disorder, and both are important to my considerations here. Both gene finding and Kendlerian molecular genetics are measures of success in the field, in my view, coupled with the translation into effective therapies or prevention measures - that is, clinical care.

How much progress has been made in the PMG as clarified above? In general, PMG investigator statements about PMG’s impact on clinical care are infrequent. However, an obvious place to start looking for statements of progress is the recent opinion piece in *Nature* by the current director of the US NIH, Francis Collins (Collins 2010). This paper addresses progress in genomic science since the announcement of a complete human genome sequence on June 26, 2000. Collins recognizes, and provides solid support for the scientific as well as economic progress in molecular genetics in the ten years following the first complete composite human genome. The consequences of genome research “for clinical medicine, however, have thus far been modest.... (acknowledging advances in cancer, macular degeneration, and predicting drug response). But it is fair to say that the Human Genome Project has not yet directly affected the health care of most individuals.” (2010, p. 674. parenthetical summary mine). In the same issue, Craig Venter is enthusiastic about the profound drop in costs of sequencing a single human genome (one of the

economic advances mentioned by Collins), later noting that one of the most important insights of the past ten years' work is "the small number of human genes – 26,000 compared with earlier estimates of up to 300,000– and the small amount of variation (0.1%) between individual humans." (Venter 2010, p. 676, citations omitted). Later turning to upcoming challenges, Venter notes that the next hurdle, phenotypes, "present a much greater challenge than genotypes because of the complexity of human biological and clinical information." (Venter 2010, p. 677) Linking phenotype with genotype will require "complete genomes of tens of thousands of humans together with comprehensive digitized phenotype data." However, he notes "Even if we had all this information today, we wouldn't be able to make use of it because we don't have the computation infrastructure to compare even thousands of genotypes and phenotypes with each other." (Venter 2010, p. 677) This reader is left wondering what we are doing with this paradigm if the abundant genetic data cannot feasibly link together genotype and phenotype. This discussion also omits the substantive issue of the relevance of phenotype-genotype coupling to the kinds of problems (mental disorders) clinicians and patients actually are concerned about. The remoteness of the psychiatric genetic phenotype to clinical diagnosis has been discussed in detail elsewhere (Sadler 2005).

In discussing a new era in psychiatric genetics for *Biological Psychiatry*, NIMH Director Thomas Insel and collaborator Lehner summarize the field: "However, 30 years of psychiatric genetics research demonstrates that high heritability does not mean ease of finding genetic causes. Indeed, the history of psychiatric genetics is largely a story of unreplicated discoveries and unrealized expectations." (2007, p. 1017; see also Züchner et al 2007). They conclude "For mental disorders with many associated alleles, we will need a wave of sequencing to identify molecular lesions and a generation of cell biology to understand their significance. If we are entering a new era in the search for genetic association, this is only the first step on a long road to mapping the risk for mental disorders." (Insel & Lehner, 2007).

Margit Burmeister, one of the leaders in psychiatric genetics, discussed progress in the field in a 2008 *Nature Review*. Burmeister notes that progress in the field has been hampered by the lack of robustness of traditional psychiatric diagnoses in gene-finding studies, also noting that locus heterogeneity (multiple genes affecting the same phenotype) complicates the field (see also McClellan and King 2010), as well as incomplete penetrance and heavy interaction with non-genetic factors are important stumbling blocks for the field. Burmeister summarizes the field by noting "... psychiatric genetics exhibits complexity at many different levels—there are diverse genetic mechanisms as well as genetic, allelic and phenotypic heterogeneity, and phenotypic pleiotropy." (2008 p. 537).

Hallmayer (2004) considers "what to expect" in the future of psychiatric genetics. He notes that future discoveries of genetic risk are likely to be of small effect size and of limited predictive value:

"Although rare and common alleles are contributing to the genetics of the psychiatric disorders studied, it will be mainly the common alleles that will be detected. Each of the predisposing alleles on their own will only contribute a small increase in risk. It is very likely that the risk will be unspecific and overlap with other disorders. It will require major efforts to define the predictive value of each of the variants ..." (p. 149–50)

In a 2010 article in *Science* discussing the future of psychiatric research, Akil et al summarize the state of psychiatric research of the last half-century: "... there have been no major breakthroughs in the treatment of schizophrenia in the past 50 years and no major

breakthroughs in the treatment of depression in the past 20 years.” (Akil et al 2010, p. 1580). This of course applies to the field as a whole, not just PMG research.

In a 2010 article entitled “Rethinking Mental Illness”, Insel and Wang conclude “With no validated biomarkers and too little in the way of novel medical treatments since 1980, families need science to provide more than hope recognizing that these are disorders of brain circuits likely caused by developmental processes shaped by a complex interplay of genetics and experience.” (Insel & Wang 2010, p. 1971)

Because my quotations are admittedly selective, I should acknowledge that despite what looks to an outside observer (me) like the leaders in the field acknowledging a miserable state of progress for etiological psychiatric research in general and PMG research in particular (if impact on clinical care is the benchmark), virtually all of the authors cited expressed great optimism and confidence in their field to prevail and provide the transformation of psychiatric practice and the treatment of mental disorders that have been long awaited. The only way I can reconcile this paradox in the literature is that all of the authors cited stood to gain or benefit by applauding their organizations’ and fields’ efforts, lest the funding stream shrink.

The scientific progress is real as technique, theory, and observations unravel molecular-level interactions. However, the therapeutic progress appears to be approaching zero after thirty years of the PMG paradigm, by the scientists’ own admission. Setting aside self-serving interests, justification for ongoing generous research funding in PMG should be based on the intrinsic value of basic research on behavioral molecular genetics, not on therapeutic promise in the treatment of mental disorders.

PMG research - How is it funded in the USA?

The United States National Institute of Mental Health is one component of the larger National Institutes of Health, which are broken into 27 Institutes and Centers that serve as “The Nation’s Medical Research Agency”. Each Institute or Center represents a particular biomedical disease entity or medical research interest, e.g, the National Cancer Institute, or, as is relevant here, the National Institute for Mental Health. NIH funds are awarded by the US Department of Health & Human Services with Congressional authority. According to the current NIH online budget information, 31.2 billion dollars are invested in medical research, 80% of that budget supports “extramural” grants to support researchers in the US and elsewhere (<http://www.nih.gov/about/budget.htm>). 10% of that budget supports “intramural” funding for scientists employed by the NIH’s Institutes and associated laboratories and clinics. The remaining 10% presumably supports NIH infrastructure.

Grant funding distributions are a complex equation of planning and serendipity. The NIH Director has a large part to play in determining the budget of component Institutes, though the Director’s decisions are always justified for Congress and subject to political arbitration. Individual component Institutes and Centers in turn use various Grant Announcement mechanisms to support particular research priorities. The most determinative is the Request for Applications (RFAs), which involves funds which have been set aside and protected for particular priority projects addressing particular social or clinical needs. Program Announcements (PAs) and Funding Opportunity Announcements (FOAs) are suggestions for submission of protocols that do not have protected budget allotments like the RFAs, but are an encouragement to submit grant proposals in a stated area. All of these grant announcements may be driven by a subject area - whether disease/disorder oriented, scientific approach oriented, or other foci of interest. “Parent Announcements” guide investigators who want to submit a proposal that is “unsolicited”, “investigator-initiated” or otherwise does not fit into the other submission-program rubrics. All grant submissions then

undergo a peer-review procedure and grant awards are intended to be based upon quality or merit. Which kinds of grants are meritorious, however, are governed by the submitting investigators with NIH guidance, and one might guess the grant review committee, usually called a “study section”, has substantive power about which grants are judged “meritorious.” Study section members are recommended for appointment on the basis of their productivity as peer investigators in the topic area. Grant program directors often make the tough choices about awards when the study section gives ambiguous guidance about merit, or the meritorious submissions overwhelm the funding allocation for the program. In summary, grant awards are determined by a social algebra consisting of NIH administrative planning, the marketplace of ideas, the science *Zeitgeist*, the social/professional dynamics of the study section, and the NIH project director.

PMG Research - How much money are we talking about?

NIH’s “Research Portfolio Online Reporting Tools (RePORT)” lists complete funding by disease entity and year. As one of the 27 Institutes and Centers of the NIH, the National Institute of Mental Health received approximately 1.17 billion dollars in funding in 2010. (“NIH Grants And Contracts - Awards and Total Funding by Budget Mechanism and NIH Institutes/Centers “ available online: <http://www.nih.gov/about/almanac/appropriations/index.htm>) of which approximately 1.13 billion dollars supported “research grants”. http://report.nih.gov/budget_and_spending/index.aspx). These NIMH research funds go to the full range of scientific research under the NIMH aegis, from basic/molecular research on up to social scientific studies relevant to the NIMH mission.

Using the NIH website, I couldn’t find a way to assess directly the funding spent on PMG, so I used the following method to estimate NIMH PMG spending for 2008 and 2009. In RePORT, a subsection on the site describes disorders by category and includes summary actual intramural/extramural funding data by principal investigator, title, funding amount, and other tracking data (<http://report.nih.gov/rcdc/categories/>). The site permits downloading of disorder-specific data into an Excel spreadsheet, which then can be sorted by inspection for projects that likely qualify as PMG projects. I selected three disorders based on PMG interest in the literature: “Schizophrenia,” “Attention Deficit Disorder,” and “Depression.” I then examined each disorders’ individual projects and characterized the ones as PMG-related using the following inclusion criteria (1) project title had relevance to gene finding or molecular-genetic mechanisms as defined by Kendler (2) project title mentioned the disorder of interest. Exclusionary criteria were more difficult and required more judgment. The exclusion criteria were (1) projects that appeared to focus on molecular neuroscience, signal transduction, and other non-genetic molecular biology, such as molecular neuroscience projects; (2) studies that were identifiable as qualifying for Kendlerian basic or advanced genetic epidemiology; (3) conference, facilities development, statistical/computing development, ARRA 2009 projects, or training grants of any kind, including those for psychiatric genetics; (4) epigenetic studies; (5) biobank support, genetic or otherwise; (6) pharmacogenomic/pharmacogenetic studies; (7) translation-error related studies; (8) studies where I was unsure of the project fit. Recognizing the limits of my characterizations by project title and the blurry boundaries between molecular genetics and other areas of molecular biology, I wanted to tip the bias balance toward excluding non-PMG projects so obtain a conservative “low-ball” estimate of PMG funding for the 2008–9 years. Only three years of record are offered on the NIH site, and for simplicity’s sake I examined only the past two completed years. Most of the projects are funded by NIMH, though other Institutes may contribute to studies involving a multiple disorders or diseases. Often the same projects are carried over to the next year, and between disorder groups occasionally the same study

will reappear, as a single study may involve two or more of my identified disorders. I didn't attempt to sort this out, the data were only provided as an estimate to raise an ethical point.

The funding allocations are summarized in Table 1 which presents an estimate of the spending for PMG by disorder, breaking out the funding in US dollars. To situate the spending in a larger context, I included a calculation for the PMG/disorder funding as a percent of the total NIMH allocation. This percentage is not fully accurate in that some Institutes other than NIMH contributed to some of the studies, elevating the percentage in some cases.

Ethical issues prompted by PMG funding

The included allocation data only approximates the scale of research funding involved in the PMG enterprise. One cannot assume that similar amounts apply to earlier years, though, so the comments below should be considered accordingly. Indeed, the marked discrepancy in total PMG allocations between 2008 and 2009 suggests the funding patterns can be quite variable from year to year.

If we consider the PMG paradigm to be roughly 30 years old, and the Human Genome Project as 10 years old, the social investment in the field should be considered against a range of other human/social interests. The United States is a country that has approximately 45 million people uninsured, and dependent upon emergency medical services as their only reliable source of medical care. Moreover, fundamental questions about ordinary service delivery in mental health care remain unanswered. For example, little is known about the cost/benefit efficacy of the standard 15-minute medication check used in the community for managing psychiatric patients on drug therapy. Comparative effectiveness studies by disorder type are only beginning to be performed and the early results show that aggregate differential benefits by one drug over another are small (Lewis & Lieberman 2008, Warden et al 2007). A major barrier to mental health outcome has been identified as access to care, which involves current, standard treatments, not innovative ones – according to major reports from the US government (Satcher 1999, President's New Freedom Commission on Mental Health, 2002). In the face of decades of limited progress for treatment of mental disorders, and in the context of these fundamental difficulties in delivering care, spending nearly 90 million dollars in two years (for only 3 disorders) in a pursuit of molecular "magic bullets" (Healy 1997, 2002) seems misguided and ethically unjustified on access-to-care comparisons alone.

The scientists involved in the PMG enterprise are careful to distinguish scientific progress and treatment progress. In this regard, the scientists' consensus appears to be that scientific progress (understanding molecular mechanisms) has been substantive while the treatment advances are marginal. This paper doesn't assess the scientific progress in the field, which is beyond the scope of the paper as well as my scientific competence. However, some of the findings of the research to date raise serious questions about the future utility of molecular genetics in psychiatric care - most notably, the computational limitation in linking phenotype to genotype under the circumstances of "best data".

For the purposes of this paper, the uncontroversial findings of the human genome project are several: (1) instead of finding several hundred thousand genes in the human genome, the current estimate is about 26,000, a fraction of earlier estimates, and the percent of human genomic variation is 0.1%. (Cohen-Woods et al 2009, Hough & Ursano 2006, Venter 2010) (2) The efficiency of the genome is much greater than expected (Cohen-Woods et al 2009, Venter 2010) - a small number of genes are doing multiple kinds of "work". (3) Gene regulation and epigenetic factors are much more important than originally expected and unraveling these introduces an even greater level of complexity than imagined ten years ago

(Collins 2010, Kendler 2005b, Kendler & Greenspan 2006, Laporte et al 2008, Li 2010, Moffitt et al 2005, Peedicayii 2002, Venter 2010). (4) Related to the gene-efficiency finding, pleiotropy (one gene influencing multiple phenotypic traits) is more widespread than expected (Ayhan et al 2009). (5) The common mental disorders such as the ones referenced in this paper are agreed to most likely involve multiple implicated genes, and perhaps up to hundreds (DeLisi et al 2006, Hallmayer 2004, Holden 2009, Keller & Miller 2006, Maher et al 2008, Owen et al 2010). (6) Replicable gene-finding techniques involve huge human samples and will be more expensive than previously thought, despite the diminishing expense of genome scanning (Abbott 2008, Arguello & Gogos 2006, Levinson 2005, Prathakanti & Weinberger 2005). (7) Insights from PMG may involve the development of gene therapies, more specific neuropharmaceuticals, proteonomic manipulations, and enriched understanding of gene-environmental effects (Hough & Ursano 2006, Li 2010).

These uncontroversial conclusions and predictions about the PMG field lead me to question the utility, and perhaps even the safety, of pursuing an aggressive PMG agenda. First of all, the gene variation in viable humans is small, and the explanatory potential of genes in isolation is small. Genomic efficiency and the ubiquity of pleiotropy suggest that actual gene manipulations would be very high risk, and that changing alleles or even modifying gene regulation of implicated alleles may have widespread “side effects” and unforeseen, likely bad, consequences. Genetic counseling and personalized mental health medicine may generate more anxiety rather than effective intervention or family planning (Khoury 2010), at least in the short run.

One wonders if a viable individual with a mental disorder involving hundreds of “abnormal” genes can genuinely be considered as having an abnormal genome, given that every human being carries multiple lethal mutations (McClelland & King, 2010). Indeed, the heritability of schizophrenia may resemble the heritability of phenotypes without pathology (and indeed may resemble the heritability of complex positive aptitudes), raising the question of whether epigenetic, post-translational, or frankly environmental interventions are the key to helping people with that disorder or group of disorders. The ethical question arising here is how long is it ethically justifiable to wait so that the myriad complexities of schizophrenia genetics and epigenetics are unraveled so that safe and effective therapies can be developed and tested? Is that waiting period justified in the face of fundamental knowledge gaps in understanding the efficacy of existing, on-the-ground mental health care? Is the waiting period justified in awaiting testing novel treatments using more mature theoretical paradigms? Are there other, faster routes to discovering effective new treatments?

Waiting for the miracle to come

David Healy, in discussing Paul Ehrlich’s coinage, explains the “magic bullet” metaphor (1997, 2002). A conventional bullet must be aimed to strike its target. A magic bullet, though, doesn’t require an aim, it finds its target by itself. The metaphor of the magic bullet appears to drive the PMG enterprise. That is, if we unravel the molecular genetic mechanisms of mental disorders we can develop gene- or signaling- or receptor-specific magic bullets that need only be introduced into the body in order to find the “enemy”- the offending biological process. The emerging realities of PMG seem to suggest that the magic bullet metaphor does not apply very well to the common mental disorders, in that molecular targets, particular pleiotropic genes, may be essential to other life functions -for the bullet to be safe it must be aimed once again.

Some revolutionary psychopharmaceuticals (chlorpromazine, fluoxetine) have been developed by industry based on molecular variations of other compounds (Healy 2002), while others have been discovered by serendipity - (lithium, imipramine, MAO inhibitors)

(Healy 1997, 2002), but all other than fluoxetine and its derivatives, and the so-called “atypical” neuroleptics were discovered over fifty years ago. After decades of drug discovery technology, from gene products to making molecular variations of preceding drugs, the failure of revolutionary new medications to appear is a puzzle. Increasing receptor binding specificities of these drugs has yielded incremental progress at best, with no revolution in therapy by the scientists’ own admission. Are we looking in the wrong places for explanations, as suggested by Insel et al (Insel 2009)? If so, will funding reprioritizing follow, and if so, will it be more of the same or truly innovative paths?

From the history of psychiatry perspective, various authors have noted the cycles of reform and neglect that have burdened the history of psychiatry and its patients (Grob & Goldman 2006, Morrissey & Goldman 1984, Sadler 2009) Conditions of the mentally ill fall so low that the public outcry is inevitable. Psychiatry responds by promising new and better treatments that are just “on the horizon.” Early failures to produce the promised improvements in care are blamed on insufficient funding, not paradigm failure. Sometimes this excuse-making is true, because of practical limitations, sometimes this kind of excuse is simply self-interested rhetoric - the answers are in the history. Mental health campaigns and conscientious reform efforts improve matters somewhat, but the expense and effort are difficult to sustain. The promised miracles never come, the public optimism weakens, and funding priorities move elsewhere, to new grand promises of miracles to come. In the meantime, the lot of the mentally ill grows worse and the cycle restarts. It’s time to reassess the PMG paradigm and be sure we are not making promises we cannot keep.

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Table 1
Estimated NIH Grant Psychiatric Molecular Genetics Expenditures by Disorder, Years 2008 and 2009*

2008	ADHD	Depression	Schizophrenia	All 3 Disorders
Total Expenditures	\$60,632,735	\$401,722,755	\$249,390,152	\$711,475,642
Molecular Genetics Expenditures	\$3,807,228	\$19,911,822	\$34,075,563	\$57,794,613
Molecular Genetics as % of Total Expenditures	6.31%	4.96%	13.66%	8.12%
2009				
Total Expenditures	\$70,944,652	\$401,962,891	\$265,237,007	\$738,144,550
Molecular Genetics Expenditures	\$2,387,788	\$10,058,416	\$20,061,433	\$32,507,637
Molecular Genetics as % of Total Expenditures	3.37%	2.50%	7.56%	4.40%

* Reflects non-ARRA funding only