February 10, 2014

Hi Jeffrey,

Thanks for taking time out of your schedule to talk on the phone and sorry for the delay in getting you this invoice. I enjoyed discussing what we can potentially do on the research side with the samples you've already submitted through the PGP.

You're probably inundated with proposals on a regular basis – so, to recap some of the general points we discussed:

1. George Church recommended me to you through your participation in the PGP and I helped with sample collection and consenting through that study.

2. You have a math background and a long history of supporting the sciences. My impression is your interests could be considered self-discovery using the latest in genomics tools: including a) sequencing, b) data analyses and storage, and c) genomic and functional manipulation of your own iPS and other cell lines. The PGP was supposed to facilitate all these pursuits.

3. To the best of my knowledge, work on your samples are on an indefinite hold with the pgp. Meanwhile, my own involvement with the PGP has weaned off in order to pursue my own genomics research study at MGH that would be decidedly more:

a) Clinical: obviously as a physician this is an important aspect for me but, perhaps even more importantly, the recent ACMG recommendations (see attached) make it obligatory for clinicians to report back incidental findings on these genes - even when sequencing was done on a healthy relative to diagnose a family member with a mutation in a different gene(s).

   Since there's no intrinsic reason to treat the genetic results of a healthy patient getting sequenced for clinical reasons (eg, a sick family member) differently from a healthy participant in a clinical genomic research study, researchers will need to strongly consider returning these results in a responsible way that helps steer research subjects toward appropriate medical management when indicated by worrisome results (especially when occurring in the 56 genes cited by the ACMG).

   These recommendations just came out summer 2013 – so you would not only be among the first getting their whole genomes sequenced; you would also be among the first getting this type of focused ACMG-guided genomic analysis.

The PGP is not a clinical study (like mine will be). Their focus is primarily on creating a large genomic database that could be publicly accessed to further genomics research. This is an important endeavor but for my interests and personal mission, it's restrictive to patients who are either (a) not interested in making their data public or (b) who are unable to properly consent to this on their own (eg, due to mental retardation). So, in general, here are the areas where my study diverges from the pgp. My study focuses on improving access and the medical utililty of an individual's genomic data – specifically in:

i) Genetics patients: maximize access and utility of next generation sequencing (ngs) in our MGH, as well as offsite, genetics patients most likely to benefit from it - regardless of their finances. (Jeffrey, sadly, ngs at MGH right now is difficult to obtain for patients without private insurance because of reimbursement issues. This isn't unique to MGH but a common issue right now across health care systems. For early technologies like this one, insurers are very arbitrary about what gets reimbursed. And most patients can't afford to pay for this out of pocket (even when the genomic test could benefit their child and the cost is only ~$1000 per sample).

ii) General public: Determine the number of healthy individuals in the general population needed to be screened with exome sequencing before 1 person has a significant medical benefit. And, maximize that clinical utility by refining the DNA sequencing and analysis pipeline over time.

b) Private: I continue to be fully supportive of George's PGP efforts but he'll be the first to admit that joining a public study is not for everyone. It's for the minority of people who are willing to take this privacy risk in the interests of science. In the case of my pediatric patients (which is a large proportion of any medical genetics practice), this was a non-starter. Not surprisingly, the pgp doesn't accept pediatric patients and this is exactly the patient population most likely to benefit from ngs sequencing.

Jeffrey, as a billionaire, you may have additional security concerns unique to that status. As you know, in 2014, our social security numbers are really not that secure. But a dna code will uniquely identify you (unless you have an identical twin(s)). I'm not advising you rule out public posting of your data. But, if you eventually pursue public posting, I think it would probably make sense to do so after we do at least one pass at detailed in-person analyses - in case anything rises to the top of your genomic variant list that gives you pause to post data publicly. (I say all this with the caveat that this is research and our current knowledge in this space is constantly evolving at a fast pace as more data comes in. So, a "first pass" analysis today could look different 1 or more years from now as

more data on genetic variants and improved software are available for genome re-interpretation.)

In contrast to the pgp, my study will start with infrastructure that safeguards privacy and will be focused on increasing the security/privacy of study participant data with genomic encryption software that are more stringent than current HIPAA regulations. Initially we will try out existing software and over time (with appropriate bioinformatic support) improve encryption with our own proprietary software.

4. We discussed this point over the phone but just so you have it in an email. Work on your samples, outside the pgp, can really only legitimately continue in one of 2 ways:
   a) Through a clinic, or
   b) Through an IRB approved human research protocol

I have and continue to order clinical exomes on my sickest patients suspected of severe genetic disease (often these are critically ill neonates). (See attached exome paper for examples of how ngs has helped in these situations.) Insurers typically reimburse in these extreme cases. I have also had private patients with personal or family history of known or suspected genetic disease in whom we ordered ngs that they paid for out of pocket.

In your case though, although we could stretch things a little and say "we're doing your genome exploration within the clinic", the cellular work will fall way outside of anything you would do in a normal clinical setting – even if you did have a serious genetic disorder.

Furthermore, going through the clinic and doing this as my patient also obligates us to have documentation in your medical record of all encounters as well as some record of your genomic data. (Raising again the issue of privacy.)

For all these reasons, my recommendation is to do all this work through the research route. (Anyone working in this space would agree with this.)

5. Assuming we're going the research route as we discussed, I'll need to get you enrolled in my study and have your samples moved from the pgp into the new mgh study (again, you can always move back into the pgp later or stay in the pgp if you want *and* enroll in my study).

   As I also mentioned, I already have IRB (institutional review board) approval as the PI for a clinical genomics study on YPO members from their Austin chapter up until completion of dna extraction. I'm personally enrolled in this study as well. So my sample will be going through the same pipeline your sample and that of participating Austin YPO members will be going through. (With the exception of your fibroblasts, adult stem cells, and other cellular work. None of the YPO people so far have fibroblasts or other cell lines, and only a very few pgp'ers (like George) have fibroblasts and/or adult stem cells.)

I still have to submit the rest of my research protocol for approval by MGH. I wanted to get your feedback on the invoice and include whatever infrastructure you're willing to provide though before submitting my proposal. Not surprisingly, the more infrastructure and funding I can cite, the more likely my proposal will get approved. If it's approved, then you, myself, and the YPO Austin members (who've already enrolled) will be completing the newly approved consent form and proceed with the research. (This will not require another online exam or be as onerous as the pgp enrollment.)

The timeline from my submitting the application is - hopefully in the next 1-2 weeks - after hearing your input on this invoice. The time from MGH receiving the application to final approval is around 5 weeks if they have no major issues with the proposal.

6. To put this work in perspective, the YPO Houston chapter collaborated with Baylor College of Medicine to produce the attached paper that I mentioned over the phone. They did "individualized" analyses based on personal and family medical history. Unfortunately their paper was submitted to the journal just before the ACMG recommendations came out this past summer. So our work (the YPO Austin chapter / Harvard Med / MGH collaboration) will have the advantage of being able to uniformly look across the same 56 genes among all these study participants. This work should lead to data that helps determine the utility of ngs when medically screening the general population – the main focus of my lab.

   The numbers may bounce around a bit at first – but, as more and more people are screened, we'll get a better handle on the "number needed to screen" before a medical benefit is seen. Over time, this number should decrease as our medical knowledge and utility of the genomic data increases. At some point, this type of screening should be reimbursed by insurers for everyone once the cost of sequencing is cost efficient and clinical utility is demonstrated.

   I can't over stress how important this work is. In my opinion, it is the most important question right now in the field.

   It pushes our timetable to the limit, but it's not out of the question to have some preliminary data – including your own, Jeffrey, to present at my Bio-It talk at 11AM on 4/30. (All data presented will be anonymized of course and only a very small fraction of any 1 individual's data (ie, a few interesting variants per subject at most) will be discussed.) See:

   http://www.bio-itworldexpo.com/Clinical-Omics/

7. That's a lot of background but I wanted to err on the side of providing more rather than less, so you know exactly how your research investment will be used.

As we discussed, if you wanted to try out the top genome analyses tools, you wouldn't be utilizing the best available at just a 1 genome throughput. Furthermore, with all the cellular work we hope to do on your existing cell lines, we should have many genomes coming from you alone

to sequence so we can answer questions like: “how is the dna sequence (and eventually rna when we’re further along) different between different cell lines (especially your adult stem cells once they’re available)?” and “how different do they get with every cell passage?”. Even more interesting, “how can we correct mutations in cell culture?”, and further down the road (year 3?) “how can we efficiently and safely propagate these corrections in vivo?”.

So, to do a really in-depth genomic analysis on 1 person across cell lines in Jan 2014 with the latest and greatest (see links to vendors below), you are, by necessity, purchasing a system that can do the same for typically 100 or more samples anyway. (Variant analyses systems that only analyze 1 genome are few and tend to be low quality.)

Jeffrey, please keep the following confidential if you don’t mind since I haven’t even shared my detailed research plans with the chief of my genetics division yet since I don’t want to get “scooped” on the idea before I have the funding needed to implement it.

In order to maximize medical utility and accessibility to ngs in the next 1-5 years, I believe the type of infrastructure I’m proposing will need to become commonplace (or, alternatively, we’ll need to be the group practically providing the service for everyone!). What I’m proposing is infrastructure *that combines 3 cutting edge areas of medicine today with untapped potential:*

a) Genomic medicine
b) Telemedicine
c) Concierge medicine

Roughly the plan is:

a) Sample collection: at a minimum: noninvasive, self collected, saliva sample from study participant after telephone or videoconferenced remote enrollment.

b) Samples may have a variety of investigations done (yours for example) but, at a minimum, all samples will have exomes sequenced (currently these research exomes can be as low as $1000 each; you will have this plus a whole genome (about $5000) through Illumina; see below).

c) All samples will go through an analysis pipeline and have a 1 time remote but “face to face” (via videoconference) with myself and a genetic counselor focused on the 56 ACMG incidental findings genes. (Though we will screen beyond the 56 genes and also look at anything indicated by the personal or family medical history.) Advice for further medical follow up will be given when indicated. My group can:

i) Help arrange this through our clinic and institution (MGH), or

ii) Let the participant pursue this with their own healthcare providers - with my group offering as much or as little assistance as the participant wants.

Even in a clinical setting a patient can ignore any advice their doctors give. Being research, this is even more the case, and all participants have the option of dropping out of the study at

any time of course. It is medical advice they would never have gotten without participating in the research afterall.

After they get sequenced and get their exome results back, all participants will then have the option of:

a) Having their data and samples destroyed with the option of receiving their own copy of the data, OR,

b) Continuing in the study. The benefits of this include: ongoing research on samples including sequencing, re-analyses (at least annually, as knowledge evolves and the acmg list grows over time), and back up storage of data. (I'm guessing you would be in this category if you participated. Would not make sense to me to invest in this infrastructure and not personally make use of it for yourself (even family, friends, loved ones) over the long term.)

This would make it the most participant-friendly genomics study I'm aware of in terms of the flexibility and options study subjects are given after return of data. I truly believe this is the direction these types of studies should be moving towards.

I don't offer a "go public" option in my study. But any participant in the study is welcome to get a copy of their own data - which they can make public on their own if they choose to do so (through the pgp or other similar efforts).

8. Let's now break this down into various tasks and where the work will be done which will be what dictates the invoice/budget for this study. I've named my study the **"Virtual Genomics Clinic" or MGH VGC Study**. The YPO data (which will also include your and my data) will be the "pilot" portion of the study that generates preliminary data necessary for publications and more long term NIH funding. I expect a total of 80-100 people enrolled in this early pilot phase of the study. If all goes well, data analysis on this group should be completed by end of May this year.

This is a first pass on your invoice broke down into categories of work and expense and where the work will be done with explanations. Where I can provide a reasonable guesstimate I do. Where a number isn't present (assuming you don't nix pursuing it), I'll get those numbers in the second version of this invoice (which should be a lot faster to generate if we're on the same page with this invoice). I've included relevant links where appropriate so it's easy for you (or someone from your group) to further drill down on details if desired.

1. **Sequencing:** cost aside, the best option right now for this is a clinical whole genome sequence from Illumina. If we can get a second whole genome for you from Complete Genomics, I would be very interested in comparing raw data concordance between the 2 platforms. I'd also like to see what CGI's new analysis suite looks like when I'm actually "driving" it. You should also have a research exome from Ambry. Which is what the YPO Austin folks and myself are having done (so we're able to compare against the same platform when analyzing you along with the YPO batch).

a) **Whole genome through Illumina:** Your best clinical wgs option today: about $5000
b) **Ambry research exome:** will run you $1000 includes research exome and some analysis from ambry; you will also get a compressed copy of your exome on memory stick through an arrangement we have with them. (This is what the ypo folks will have done.)
c) **Complete Genommics/BGI:** I would say (a) and (b) above should definitely be done given your resources and interests. (c) is optional but it would be nice to check concordance with Illumina's data. Not enough groups have done this and it would be great to include this data in a publication. There really isn't enough of this type of validation in the medical literature. (This is partly because CGI does their sequencing as a service. And their proprietary instrument is "black box".) I don't have a number from them yet. But I don't think it will be more than $5000 for a whole genome.

2. **Raw data analysis and storage:** What I'm envisioning for you and other study VGC participants is a dedicated room at MGH's Center for Human Genomics Research Center that houses our genomic servers and doubles as a mini-exam and consultation room where results are returned either in person (if they happen to be in Boston) or via videolink.

I divide this into 2 main platforms:

a) **onsite servers** (there are ***3*** commercial vendors whose products I think are worth purchasing and assessing; each of these are loaded up with their own proprietary genomic analyses software), AND

b) **genomic analyses software suites**: ***6*** of these worth pursuing in my opinion. There are more but the functionality starts to either overlap with these other 6 (or I don't trust the science from the people putting out the product so I didn't bother listing it).

3. **individualized cellular and functional studies of your own cells (including adult stem cell generation and genomic manipulation/engineering of personal cells):** We should be able to get your fibroblasts differentiated into adult stem cells at Boston Childrens Hospital through the lab of my old mentor, Gerry Berry, the head of biochemical genetics there and previous president of the SIMD.

http://www.childrenshospital.org/research-and-innovation/research-labs/manton-center-for-orphan-disease-research/senior-scientist-program/gerard-t-berry-md

http://www.simd.org/Index.asp

a) Jeffery, at cost, you could get your cells turned into adult stem cells through a company and that would run $15K. But they would just hand you back the cell cultures and essentially no research would be ongoing with them.

b) Gerry Berry's lab can do the same for $15K but there will be some overhead/indirect costs for the work being done at Childrens. And from discussing the cellular work

with Gerry, I do know he is worried about the actual manpower – the funding for their postdoc doing the actual cell cultures (not just yours).

I personally know the postdoc in his lab doing the iPS cell (induced pluripotent cell or adult stem cell) work and she's excellent but her research funding has dried up and Berry lab really wants to keep her. I promised I would ask you if this was something you'd be willing to support.

You should know that this isn't an expense you would have through a commercial vendor. Under normal circumstances, I also think it's a little unreasonable to ask you to cover the salary of the person working on your cells.

Still, if you were willing, they are only asking for 2 years salary – which would also support her as she completed biochemical genetics training. And you would of course get regular updates on what was happening with your cells and she would have the devoted time to keep a variety of studies going on your cells (guided by your sequence data). Her salary would be: $50-60k/yr X2 years.

4. **Indirect costs at HMS, MGH, and Boston Childrens**: I'm sure you're familiar with this next category of cost. It's one I still have a hard time justifying – not in principle but because of the large proportion that gets taken out from a total budget. I'm referring to the ridiculous 60-70% "indirect costs" HMS, MGH, Childrens' Hospital, and any academic center routinely takes out of research grants. There are mechanisms for avoiding this with private grants like yours though and we'll pursue this. (Ie, bringing the money into a large research pool with the understanding that your money is specifically used for our genomic study (MGH VGC) is one way of doing this.)

   In previous conversations, I did mention doing any work for you pro bono but I've been told MGH/CHB/HMS will want my research effort appropriately covered for the appropriate %effort I devote on any grants I accept (which allows the respective institutions to proportionately decrease their own level of support for me).

   So, that provides most of the basics for understanding the invoice below broken down into the categories above. My apologies again for all the text.

   Here is the general breakdown along with some clarifications. Remaining itemized costs will get filled in over the next week after I get some feedback from you:

   INVOICE:

I. **Sequencing:** = ~$11,000 total

WGS through Illumina: $5,000
Exome through Ambry: $1,000
2nd WGS through CGI/BGI: $5,000

II. **Analysis suites / private, restricted access MGH VGC genomics server room next door to an exam room and office**.

= $190k/yr for personnel (see below) + MGH indirect costs for the space rental (to be determined) + server costs X3 (to be determined) + analyses software costs X 6 (to be determined)

1. MGH indirect costs: Not sure what this will be. I want this to be zero – and this may be possible. Indirect costs do include space rental though and that cost will remain so I'll look into what space for this work will run us for 1-3 years.

   Ideally, our space will be rented within MGH for this research project and include:
   - 1 server room
   - 1 study office
   - 1 exam room

Your support could provide the bridge funding needed for 1-3 years until other sources (NIH grants, etc.) can pick up expenses after we publish our initial findings and our effort gets on the map.

2. Personnel: to really do this right and keep things on track, a few hires would really make this effort a reality:

a) A bioinformatician: I think we can get away with part-time help here: $30K/year for <50% effort to insure IT systems are running smoothly and communicating with each other; as we are further along this person will potentially build out proprietary, inhouse analyses tools that are an improvement and hybrid version of what we evaluated in year 1 (and found most useful).

b) Genetic counselor: this person will serve as our study coordinator and help with pre- and post-test counseling. He/she will also help me with clinical duties as responsibilities increase on the research you would be supporting. Full time: $60k/yr.

c) My own effort: 2 days/week specifically for this research (in realty my effort will be more than 2 days/week). Given a $250K/yr base salary, this would be $100k/yr for me OR 40% effort. (What proportion of this $100K/yr would be going through MGH and what will be going through Boston Childrens Hospital would still need to be determined.)

3. Servers: These are relatively big ticket items. Each server will be a few grand. Three are top on my wishlist right now:
   a) Bina: http://www.binatechnologies.com/product
   b) CLC bio: http://www.clcbio.com/products/clc-genomics-server/

c) Genomatix: http://www.genomatix.de/solutions/genomatix-mining-station.html

4. Software suite vendors: These won't be as bad costwise – but there are 6 of these I would get. Some of these have free versions but those versions lack a lot enough bells and whistles to really limit utility (probably why it's free) and can't be used on more than a few genomes. I would purchase and evaluate the premium versions of these 6.
   a) Cartagenia: http://www.cartagenia.com/
   b) DNA nexus: https://www.dnanexus.com/
   c) GeneTalk: http://www.gene-talk.de/
   d) Appistry: http://www.appistry.com/
   e) NextCODE Health: http://www.nextcode.com/
   f) BC Platforms: http://www.bcplatforms.com/

5. Functional studies, stem cell, and other cellular work: This will be happening at Boston Childrens Hospital. And I've already discussed it with my old mentor, Gerry Berry, and he agrees to it.

= $15K + 60K = $75k/yr

a) Cost for reagents and other essentials: $15K for transformation of your fibros to iPS cell lines

b) Obviously, you went with a commercial vendor through a commercial vendor, the work could be done without you funding a postdoc at Boston Childrens. That said, if you were able to fund this PhD (and way over-qualified tech), she would be able to fund her own a biochemical training while working on your cells as part of her required research work. The lab would be indebted to you and I think you would get very good service and research on your cells doing this if it's possible. (The Berry lab protocols originate from George Daley's lab – arguably the foremost authority on adult stem cells. Daley lab is also where George Church lab got their iPS protocols.) Her salary = $60K/yr (X 2 yrs so she can complete her training.)

Everything I've described above pertains mainly to year 1 of our MGH VGC project. Much of these total costs are paid upfront too. (eg, the sequencing of cells can occur at a slower pace after your exome and wgs x2 is done; and servers are a year 1 purchase).

If this sounds good to you so far, in addition to a highly innovative hybrid of genomics/tele/concierge medicine, the long term goal of the fledgling Thakuria lab beyond increasing access, medical utility, and refinement of clinical ngs workflow, is to essentially be an independent clinical investigator lab with ngs medical discovery throughput that rivals the biggest genomic centers (eg, Sanger Centre, Max Planck, the Broad, etc). It's only through

recent advances in instrumentation that keeps this from sounding crazy and actually implementable – on a desktop sequencer.

See:
http://www.illumina.com/systems/nextseq-sequencer.ilmn

It might sound aggressive but with adequate funding it's very much within reach. The timeline would be:

1. Year 1(2014): Offsite sequencing; onsite genomic data storage and analysis; iPS cell line generation.

   First half of 2014. We nail down the analysis and storage of the sequencing data generated on you and participating YPO members (Austin chapter; I have around 80 enrolled right now). By June 2014, the first wave of initial analysis and individual return of results to all participants is completed (completing our pilot phase). Bills are paid for space and essential personnel.

   Second half of 2014 (July-Dec): Publish prelim data. Increase enrollment numbers. Apply for grants with prelim data.

2. Year 2 (2015): Early 2015: 2nd data release. Trim down analyses tools and servers to those 1 or 2 with the best functionality and UI. Begin work on inhouse server construction, and proprietary analysis and genomic visualization software. Improve videoconferencing capabilities and subject phenotyping. Start to build inhouse capabilities to remotely collect EKG, EEG, sleep study, and other real time medical data. With iPS cells available from year 1 (at this point, Jeffrey, you may only be 1 of 6 people I currently have iPS cells on so you can expect extensive studies on them) begin work differentiating into neurons and other cell lines. Collaborate with the Wyss so we can do "organ on a chip" experiments. Begin genomic engineering using CRISPR and other technologies to correct mutations in vivo with model organisms. Begin using zebrafish for these studies. (Jeffrey, this is an inexpensive yet very effective animal model. Initial investment for a fully functional zebrafish lab is only around $15K/yr.) Begin RNA analyses (transcriptomes) on some VGC subjects as resources allow. End of year 2, 3rd data release.

3. Year 3 (2016): Move sequencing inhouse/onsite at MGH with the latest version of:

   http://www.illumina.com/systems/nextseq-sequencer.ilmn

   Continue year 1 and 2 work. Add personnel as resources allow. Add a robot for UI and videoconferencing. I initially thought the robot may be a little over the top and may not provide value proportional to the cost of the robot. See:

   http://www.cio.com/article/732223/Healthcare_Robot_Brings_Experts_to_Bedside

My thinking was some of this robot's functionality can be achieved with a simple videoconferencing hookup – albeit without the diagnostic tools. The $4K/month price tag to lease is steep but I'm sure we can get a better deal on it (especially citing our study and the institution we would be conducting research at). Cost aside, I do think this is something our sick MGH kids would really enjoy (interacting with a robot!) and consulting with remote experts is something we regularly do with our genetics patients. If it's not already obvious, doing my genetic patient rounds with this robot is clearly the most optional item on the invoice. It is also the most expensive item on the invoice with the exception of a desktop next gen DNA sequencer in year 3. Which would run at least $150K if we are bringing sequencing capability inhouse.

I can provide a detailed invoice on years 2 and 3 after feedback from you on the year 1 proposal. Again, most of the expenses are front loaded in year 1. The only other really big ticket item would be a sequencer in year 3 (~$150K to have our own sequencer) +/- a robot.

So here's the breakdown for year 1. Jeffrey, this is essentially lays out what I want to do over the lifetime of my research career. This is why my % effort is 40%.:

1. Sequencing:
   WGS from Illumina = $5000
   Ambry exome: $1000
   CGI genome: $5000
   Total = $11,000

2. Bioinformatics infrastructure: 3 servers + 6 analyses programs. I need to drill down on these costs more, Jeffrey, but assuming $5-10K/server (let's say $10K/server or $30K total) and $3K/analyses platform (or $18K total).
   Total = $48K.

3. Adult stem cell, genomic engineering, and other cellular work: $15K for reagents only; $60K X2 years for a postdoc personally working on your cells and reporting to you on a regular basis. I don't want to promise anything this early on, Jeffrey, but it seems reasonable to me that our analysis of your data and work on your cells would be something that would evolve over time guided by your own health status. Adequate personnel insures this level of attention.
   Total $15K + $60K = $75K (same level of support for cellular work in year 2)

4. Personnel:
   a) Bioinformatician: part time $30K/yr
   b) Genetic counselor: $60K/yr
   c) My 40% effort or $100K/yr (required by my instituitions; and frees me up from clinical time to effectively pursue this research)
      Total personnel = $190K/yr (same level of support for personnel in year 2)

Grand total for year 1 (excluding indirect costs) = $324K/yr

Costs in year 2 should be less than $324K/yr

Costs in year 3 go up if we add in our own sequencing capability (additional $150K-200K/yr) +/- a robot.

Cost above does not include "indirect costs" from MGH, CHB, or HMS but I'm looking into ways to avoid this being charged. We will need to cover space rental though for the servers and perhaps one study office and study exam room if possible.

As I discussed, the MGH Virtual Genomics Clinic study is happening regardless and the goal would be that your initial funding would get us the initial data and publications to fund the project indefinitely. It's possible that we're independent from your funding by Year 2. Or alternatively, we could continue receiving your funding in addition to other sources and step up our timeline.

If you wanted to make a larger up front investment (eg take care of years 1-3), we could step things up so that inhouse sequencing (with access for you, underinsured MGH patients, and anyone of your choosing (eg, family/friends who are willing to participate)) is available through Thakuria lab at MGH by Fall/Winter of this year. The in vivo animal model studies on zebrafish could also begin in year 1 (for ~$15K investment) rather than in year 2. (ie, this would be introducing mutation(s) found in our subjects into zebrafish and observing as well as correcting the mutation in a live organism.)

I'm going to end here. Let me know what you think. With the invoice above, you can imagine a stripped down version covering only the work on your samples. (eg, no onsite servers, no personnel other than my own effort, minimal analyses tools) With the invoice though, you should get a sense for what gets affected with every cut (including delays in our timeline).

Jeffrey, thanks for your valuable time and willingness to hear this proposal. I'm feeling guilty about writing such a long proposal but hopefully some of these details are helpful. It is a very ambitious project but I think you ideally want all the moving pieces in 1 place to be successful in this space.

I don't know to what extent if any you've looked in to my work and credentials. I wrote the chapter on "Clinical Interpretation of Genomic Data" in the recently published American College of Physicians textbook, "Clinical Genomics" that just came out this winter. It is the only genomics textbook the ACP has out out.

https://store.acponline.org/ebizatpro/ProductsandServices/BooksfromACPPress/ACPPressDetail/tabid/203/Default.aspx?ProductId=21146

Jeffrey, you can find my mgh web profile here:

http://www.massgeneral.org/doctors/doctor.aspx?id=18287

(I need to spend a little time adding my pic and other info to it to jazz it up sometime soon. I'm also due to be upgraded 2 notches from instructor to associate professor at HMS and MGH. I've met all the requirements – I just need to complete and submit some paperwork.)

And here's one of my hms profiles with a partial listing of my publications:

http://connects.catalyst.harvard.edu/Profiles/display/Person/8411

Being an internal news (rather than scientific) publication, this shouldn't carry a lot of weight but I was also in this piece in the last issue of Harvard Med magazine. (see attached pdf) So, this gives you an idea of how timely this type of work is.

I've also attached my NIH biosketch for your reference.

Lastly, my first author publication, Back to the Future: From Genome to Metabolome, gives you an idea of the type of individualized analyses we could do on the biochemical side using an individual's genomic data to guide us. Potentially leading to customized diets in the future.

Thanks again, Jeffrey. Look forward to hearing from you after you've had a chance to review the material. Email or call my cell anytime with questions or clarifications at 917-774-3346.

Sincerely,
Joe Thakuria

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