FYI

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From: ████████ <████████████████>
Date: Mon, Aug 28, 2017 at 10:18 PM
Subject: Alzheimer's
To: Bill Gates <████████>, Larry Cohen <████████████████>

Bill and Larry - hi. And just to you both - I will send to the others and copy Larry later tonight.

As promised, below and attached are my thoughts on a possible learning initiative for Alzheimer's disease. If there are magic new ideas I will send them along later.

10 things to do = $100 million = 3 years. I've included every detail so that you can easily plug and play if you wanted. Super easy to manage this from bgc3, quietly.

Given my experience building and managing learning initiatives and my understanding of this landscape, I've tried to think about your competitive/comparative advantage while giving you a little more time to learn in the background.

At the end of this learning you could exit the space easily, go deeper or even change strategies based on what you learn. In 2-3 years a few things will unfold - and I would just caution you to tread lightly because all sorts of new data is emerging - not only about mechanisms of disease but about whether AD is a distinct pathologic entity. Lord knows = I just don't want you to get caught into a polio type vortex until you are ready.

McKinsey has been hired to help build your strategy and I will pass all of this along to the McKinsey team, Bose and Jonah under separate cover. I will also continue to support them, make introductions and join their sessions - next one September 8. In my honest opinion, McKinsey maybe not the right partner but we will all rally behind them.

Thanks for the opportunity to contribute to the discussion - let me know if you have questions. Israel trip report coming later in the week when Bose/Gilla have had a chance to review. Some really cool science but 2 or 3 tech things to watch for sure.

See you both soon... M

Aspiration

1. Segment the landscape until we have a natural advantage

2. Opportunities small enough to win, large enough to matter

3. Measurable points on the board

Situation

- Alzheimer's is not a typical disease with a single causal factor / etiology

- Polarized scientific community

- No shortage of R&D resources

- Requires longitudinal investments in health and hard to quantitatively track pathology

- What needs fixing

    o Institutions – processes, policies

    o Tools & technologies – validation, standardization

    o Science – exploration, cross-sector ideas

Informed Entry into Alzheimer's Landscape

$100 million, 3 year learning initiative managed *quietly* from bgc3 that will explore:

1. Performance of existing institutions vs. need for creation of new (or hybridized) ones

2. Opportunities for cost savings and market building

3. Barriers to clinical trial participation

4. Processes for data sharing and standardization

5. Novel mechanistic approaches

Specific Targets for Exploration

Target 1: Underwrite risk for private sector; keep data in the public domain

Cost	$20 million
Recipient	AMC-AD, National Institutes on Aging (NIA)
Form	Matching grant (1:2 for government, 1:1 for private sector)
Proposed Outcomes	· In 3 years, study and trial data for 2016++ pipeline fully public and curated by NIA · Stronger NIA · Open trial data · 10 new candidate drugs put into later stage discovery process
What we learn	· Strength of NIA in a leading role · Value of public-private push

Target 2: Create a world biomarker consortium

Cost	$10 million
Recipient	Giovanni Frisoni, University of Geneva, Geneva, Switzerland
Form	Grant Possible Partner: IMI
Proposed Outcomes	· In 3 years, 5 validate biomarkers · Standardized validation processes · Open and shared trial and registry data · Aligned US/Europe regulatory and study processes
What we learn	· Coherence of standards · Appetite for shared data · Ability of new institution to attract additional resources

Target 3: Build microbiomic fundamentals

Cost	$20 million across 3 recipients
Recipient	1. $5m to NIA/NIH to RFP pre-inflammatory and inflammatory markers ($5m) 2. $5m to ICDDR,█ to classify non-pathogenic colonists and create a digital library 3. $10m TBC via BMGF to redraw bacterial taxonomy based on genetic criteria to supplement traditional identification and classification
Form	Grants
Proposed Outcomes	· Identify non-pathogenic colonist strains for use in health and also food and supplement indusitry · World Gut library · Update bacterial classification systems to include genomics
What we learn	· Build a deeper understanding of the microbiome with applications across health, pharma and food sciences · Modern bacterial taxonomy based on genetic characteristics · Microbiome non-pathogenic library offers biomarkers for health but also potential prebiotic and endobiotic candidates for food and pharmaceutical industries (monetizable = creates new market)

Target 4: Invest in computational repurposing of failed candidate drugs

Cost	$18 million
Recipient	TBC 1. $1m scoping (go/no go) effort with McKinsey 2. $2m pilot 3. $15m initial investment in repurposing fund either as part of a new entity versus within the NIA AMP-AD

Form	1 contract, 1 grant and 1 investment
Proposed Outcomes	· Scope potential of market and collaboration with McKinsey · 20 repurposed medications · Creates new market opportunity for failed drugs
What we learn	· Possibility of creating a for-profit (revenue sharing) institution · Potential for sharing trial data · Value of failed trials and drug candidates

Target 5: Investigate and build social biomarkers correlated with aging and dementia

Cost	$2 million
Recipient	Israel Brain Technologies
Form	Grant for Grand Challenge-style competition
Proposed Outcomes	· Candidate digital biomarkers · Financial and social safety nets for at risk (early detection or red flagging)
What we learn	· Scale and scope of potential for digital biomarkers in cognitive disease

Target 6: Bring the financial industry into the conversation

Cost	$1 million
Recipient	$1 million to Dr. Jason Karlawish at University of Pennsylvania Medical School / Wharton School
Form	Grant
Proposed Outcomes	· Explore financial behaviors of senior investors *Wealthcare* alongside the Fed, FDIC · Feasibility study for creation of long term care insurance for caregivers (*not just facilities = insure against you having to care for someone or to pay you to do it*) and relieve burden on long term facility care insurance providers
What we learn	· Possibility of using financial markets to reduce cost and ease burden of care · Create a new financial product

	· Create automated checks and balances or financial standards for demented adults or retirees over age 65 with cognitive challenges · Share actuarial burden between long term facility care-caregivers

Target 7: Reduce CMS facility and hospital admission costs

Cost	$1 million
Recipient	RAND
Form	Grant
Proposed Outcomes	· Cost : benefit analysis for CMS to classify cognition and safety as skilled medical needs · Shape financial argument for CMS reimbursement for cognitive home health nurses (like hospice nurses)
What we learn	· Save tons of money · Reduce hospital admissions · Share burden of care

Target 8: Improve trial enrollment

Cost	$2 million
Recipient	Lon Schneider, USC School of Medicine
Form	Grant
Proposed Outcomes	· Linkage across trials · Improved (and shared) recruiting tools · Corporate advocacy · Involvement of search engines (Google, Bing, etc) in stacking searches
What we learn	· Barriers to participation · Corporate appetite to contribute · Institutional appetite to widen trials and/or share controls

Target 9: Novel mechanisms for exploration

Cost	$25 million
Recipient	Either via intermediary such as Cure Alzheimer's Fund or 8-10 individual recipients (see below)

Form	Grant
Proposed Outcomes	· Immediate and unbounded support for scientists exploring alternative mechanisms from $1-5m each
What we learn	· Dysregulation of neural pH dynamics: Aimee Kao, Ph.D. / University of California, San Francisco · Human age equivalency and functional phenotypes: Fred "Rusty" Gage, Ph.D. / Salk Institute for Biological Studies · Gliovascular changes and waste (glymphatics): Jeffrey Iliff, Ph.D. and William Rooney, Ph.D. / Oregon Health & Science University · White matter dysfunction as a biosensor: Ragnhildur Thóra Káradóttir, Ph.D. / University of Cambridge · Cellular networks controlling proteinopathy: Martin Kampmann, Ph.D., Michael Keiser, Ph.D., David Kokel, Ph.D. / University of California, San Francisco · Immunological gating pathways and denegeration: Dr. Michael Schwartz / Weizmann Institute · Rejuvenation of the nervous and vascular systems: Dr. Shai Efrati / Sagol Center · Filamentous bacteriophages as therapeutics: Proclara biosciences (may be better fit for DDF)

Target 10: Convene a 3 year Task Force to guide your learning

Cost	$ 1 million
Recipient	NACC, Dr. Bud Kukull / University of Washington
Form	Grant
Proposed Outcomes	· Annual convening and quarterly check in to review NACC data, status of trials and potentially inputs from Targets 1-9 as listed above
What we learn	· Expert opinion(s) on emerging data, trends and science

	· Progress and perspective on our own learning from Targets 1-9 as listed above

Managing the Process

Cost	$ 500,000 per year
Recipient	TBC
Form	Contractor or Staff (bgC3) as under the radar manager or advisor + .25 FTE administrative support
Proposed Process	· Perform due diligence on proposals · Manage portfolio of learning grants (and contracts) · Report to Bose/Jonah/Larry quarterly or as required otherwise · Attend or delegate attendance for major meetings · Submit quarterly summary report and annual learning report · Serve as primary point of contact with partners / quarterly calls