

Public Written Comments

Submitted to PCAST
September 10, 2013 - November 18, 2013

As specified in the Federal Register Notice, because PCAST operates under the Federal Advisory Committee Act (FACA), all public comments and/or presentations will be treated as public documents and will be made available for public inspection, including being posted on the PCAST website.

Urgent: Please stop HHS from contracting with the IOM to redefine M.E.

From: "Hope Jones" [REDACTED]
Date: Wed, September 18, 2013 6:28 pm
To: pcast@ostp.gov
Cc: [REDACTED]

Dear Sir/Madam,

I am disheartened to hear that HHS is once again pursuing a contract with the Institute of Medicine (IOM). Since I was diagnosed in 2007 with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), I have had to deal with the bias, indifference, and ignorance of medical providers who try to characterize my illness as a mental disorder. Consequently, my health has deteriorated and I am no longer working. Any case definition that the IOM produces is likely to undermine the work of ME/CFS experts, leading to further marginalization. Does the government not want patients to have a real opportunity to improve their symptoms and/or recover and return to the workforce?

ME has been classified as a neurological disease by the World Health Organization (WHO) since 1969 (WHO ICD code 93.3). However, in the US, the Department of Health and Human Services (HHS) promotes an excessively broad view of the disease and conflates it with "Chronic Fatigue Syndrome" ("CFS"). "CFS" is a social construct created by a government committee in 1988 based on a cursory investigation of an outbreak of ME in Lake Tahoe, Nevada by the Centers for Disease Control and Prevention (CDC). According to the physicians and patients who were affected by this outbreak, patients were not examined and abnormal test results were ignored. This has confounded ME with depression, deconditioning and nonspecific chronic fatigue, has severely impeded research, and is the direct cause of the medical skepticism and inappropriate or harmful treatment recommendations to which patients are subjected.

Now HHS is intent on redefining ME again using the Institute of Medicine (IOM), an organization whose former President, Dr. Kenneth Shine, has stated it is highly unusual for the IOM to be asked to define a disease. The first time IOM was contracted to do this was earlier this year -- to define Gulf War Illness (GWI). The GWI IOM study group includes people with well-known biases as well as members unfamiliar with the disease. It is harshly criticized by GWI advocates as a previous IOM report referred to GWI as "Chronic Multi-Symptom Illness", a symptom based syndrome defined so broadly that half the US population could be diagnosed with it.

HHS has repeatedly stated its intent to similarly use non-experts to define ME. This is a very serious concern for patients who face widespread disbelief every day from the general medical and research community. It is also inexplicable given that researchers and clinicians with years of experience in studying and treating this disease have already created two peer-reviewed case definitions, the 2011 ME International Consensus Criteria (ME-ICC) and the 2003 Canadian Consensus Criteria (CCC). Both are accompanied by clinical guidelines for medical practitioners, and are well regarded by patients, ME doctors, and ME researchers.

In defiance of President Obama's Open Government Initiative, HHS is pursuing the IOM contract unilaterally and with disregard for the overwhelming opposition to it from the ME community and advice from its own "Chronic Fatigue Syndrome" Advisory Committee (CFSAC). I have been emailing HHS daily ever since I found out about the IOM contract solicitation to ask the Department to stop it.

I thought I was heard when, at one point, the contract solicitation was modified to read, "Because of all of the concern from the public surrounding this potential sole source requisition, we have decided to discontinue this request", followed shortly thereafter by the statement, "This request has been cancelled. However, HHS will continue to explore mechanisms to accomplish this work." But on September 12, the ME community was informed (via a listserv) that HHS will "continue to work on a contract with the Institute of Medicine (IOM) to develop recommendations for clinical diagnostic criteria. When the contract is completed, we will provide additional information via the CFSAC listserv and website. This topic will be included as an agenda item for the November (CFSAC) webinar." And now, I've learned that HHS plans to finalize the

contract by September 30!

I beg you to intervene and stop HHS from pursuing this contract. Instead, please ask HHS to use the funds set aside for an IOM study group (which will, according to IOM's own standards, include people unfamiliar with ME), to facilitate meetings of ME researchers and clinicians who have the needed expertise to agree on scientifically testable biomarkers, understand the pathophysiology of the disease, and identify treatment approaches.

Sincerely,

Hope Jones, JD

**Hope M. Jones, J.D. Class of 2010
University of the District of Columbia
David A. Clarke School of Law**

"Never forget that everything Hitler did in Germany was legal." -MLK

YOU MUST Stop the IOM Contract to Redefine ME/CFS

From: "Claudia Goodell" [REDACTED]
Date: Fri, September 20, 2013 11:36 am
To: pcast@ostp.gov

Dr. Holdren,

The Department of Health and Human Services, acting through the Office of the Assistant Secretary, is unilaterally pursuing a contract with the Institute of Medicine to redefine ME/CFS, despite the objections of the affected patient community and without informing members of your federal advisory committee for the disease. I have no alternative but to ask that you stop this contract and listen to the subject matter experts on this disease. OASH recently published a sole source solicitation for the Institute of Medicine to “develop consensus clinical diagnostic criteria for this disorder.” The request was swiftly cancelled after ME/CFS advocates objected to the backroom secrecy, short response time, and the IOM’s patent lack of experience in creating accurate and meaningful case definitions for diseases. Despite those objections, OASH has stated its intention to sign this contract (without publishing a sole source notice) by September 30th.

The appointed CFS Advisory Committee recommended to convene a “stakeholders’ (ME/CFS experts, patients, advocates) workshop in consultation with CFSAC members to reach consensus for a case definition useful for research, diagnosis and treatment of ME/CFS beginning with the 2003 Canadian Consensus Document case definition and its utility for diagnosis and treatment of ME/CFS.” *CFS Advisory Committee recommendation, October 2012*. Not only has the recommendation been ignored, but OASH has concealed the plans for this IOM contract from the voting members of the Advisory Committee.

The DHHS is progressing on a contract to the IOM with no assurance that the actual clinical and research ME/CFS experts would be the ones staffing the consensus panel. This Department has concealed its plans from the public and your own Advisory Committee. This Department is pursuing this despite the overwhelming objections of the ME/CFS community.

I have no confidence that this Department and its agencies will act to protect me or to ensure that I can receive accurate diagnosis and adequate treatment of my disease. Your agencies and personnel have repeatedly ignored the hallmark symptoms of this disease, disregarded the case definitions authored by ME/CFS experts, and resisted meaningful engagement to address the scientific questions that have plagued this disease for decades. This latest episode has only increased, rather than allayed, my concerns. This Department has failed to act in good faith at every opportunity in the last month, and I have no choice but to oppose this.

I urge you to consult with the researchers and clinicians who have actually worked on ME/CFS, and not rely on those with no direct experience or whose expertise is limited to overlapping or related conditions. We need transparency, accountability, and direct consultation with the experts, patients and advocates in order to have any hope of moving forward with an accurate case definition for ME/CFS. At present, this Department is only creating barriers to meaningful progress.

I ask that you stop this IOM contract. I ask that you bring all the stakeholders to the table to address this situation as equals. The climate of mistrust and bad dealing that these actions have created will haunt us for years to come, and a case definition that does not reflect the disease will set back research and treatment efforts for decades. None of us can afford for this Department to get this wrong.

Sincerely,
Claudia Goodell

Redefine ME

From: Sandrine Bégin [REDACTED]

Date: Sun, September 22, 2013 6:15 pm

To: pcast@ostp.gov

Dear _membres of OSTP_____,

HHS has stated it intends to sign a contract with IOM to redefine my disease by September 30!
Please intervene as soon as possible and tell the Department not to do this.

I have been personally touched by the devastating disease, Myalgic Encephalomyelitis (ME). ME has been classified as a neurological disease by the World Health Organization (WHO) since 1969 (WHO ICD code 93.3). However, in the US, the Department of Health and Human Services (HHS) promotes an excessively broad view of the disease and conflates it with "Chronic Fatigue Syndrome" ("CFS"). "CFS" is a social construct created by a government committee in 1988 based on a cursory investigation of an outbreak of ME in Lake Tahoe, Nevada by the Centers for Disease Control and Prevention (CDC). According to the physicians and patients who were affected by this outbreak, patients were not examined and abnormal test results were ignored. This has confounded ME with depression, deconditioning and nonspecific chronic fatigue, has severely impeded research, and is the direct cause of the medical skepticism and inappropriate or harmful treatment recommendations to which patients are subjected.

Now HHS is intent on redefining ME again using the Institute of Medicine (IOM), an organization whose former President, Dr. Kenneth Shine, has stated it is highly unusual for the IOM to be asked to define a disease. The first time IOM was contracted to do this was earlier this year -- to define Gulf War Illness (GWI). The GWI IOM study group includes people with well-known biases as well as members unfamiliar with the disease. It is harshly criticized by GWI advocates as the charge of this study is to fold GWI into "Chronic Multi-Symptom Illness", a made-up syndrome defined so broadly that half the US population could be diagnosed with it.

HHS has repeatedly stated its intent to similarly use non-experts to define ME. This is a very serious concern for patients who face widespread disbelief every day from the general medical and research community. It is also inexplicable given that researchers and clinicians with years of experience in studying and treating this disease have already created two peer-reviewed case definitions, the 2011 ME International Consensus Criteria (ME-ICC) and the 2003 Canadian Consensus Criteria (CCC). Both are accompanied by clinical guidelines for medical practitioners, and are well regarded by patients, ME doctors, and ME researchers.

In defiance of President Obama's Open Government Initiative, HHS is pursuing the IOM contract unilaterally and with disregard for the overwhelming opposition to it from the ME community and advice from its own "Chronic Fatigue Syndrome" Advisory Committee (CFSAC). I have been emailing HHS daily ever since I found out about the IOM contract solicitation to ask the Department to stop it.

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September 12, the ME community was informed (via a listserv) that HHS will “continue to work on a contract with the Institute of Medicine (IOM) to develop recommendations for clinical diagnostic criteria. When the contract is completed, we will provide additional information via the CFSAC listserv and website. This topic will be included as an agenda item for the November (CFSAC) webinar.” And now, I've learned that HHS plans to finalize the contract by September 30!

I beg you to intervene and stop HHS from pursuing the IOM contract to redefine my disease. Ask HHS to use this money instead to set aside funds for research based on the criteria ME experts have already created. This would drive the sorely-needed aggressive campaign to validate biomarkers, understand the pathophysiology of the disease, and identify treatment approaches.

Sincerely,

Claudine Prud'homme

Reduction of greenhouse gas emissions

From: "KAPHIRI SAPALA" [REDACTED]
Date: Wed, September 25, 2013 4:55 am
To: pcast@ostp.gov

hi
please see the document attached and the relevant research.

i eagerly await your feedback .

Sapala K.

Diagram of the type of the conrodes to be fitted for the connection of the pistons to the crank shaft.

FROM : Scientist Kaphiri Sapala
Nationality : Malawian
Present City : Johannesburg
TO : Senior Advisor to President Barack Obama on Science and Technology.
Copy to : Chief Technology Officer of Greenhouse Gas Emissions Reduction, White House.

SUMMARY:

THE DISCOVERY OF TECHNICAL CLEAN ENERGY IN ENGINES TO BE USED AS A SCIENTIFIC AND TECHNICAL METHOD AS A SOLUTION OF THE 70% REDUCTION OF GREEN HOUSE GAS EMISSIONS AS THE NO 1 GOAL OF THE US PRESIDENT.

1. As the president, as your committed to reduce greenhouse gas emissions, as a young Scientist, I am here by with the information about the discovery of clean energy in engines which will help to reduce CO2.
2. The discovery of energy has been satisfactory achieved after my personal involvement in critical scientific research in engine for the objection to find solutions for the reduction of greenhouse gas emissions. Mostly I have been dealing with the physics of the crank shafts and the pistons from 2001.
3. In order to discover energy firstly I have discovered the TECHNICAL V ENGINE with MULTI-TRANSMISSION ENERGY SYSTEM as given in the picture WY.

PICTURE OF THE TECHNICAL V 60 WITH MULTI-TRANSMISSION ENERGY SYSTEM.



Diagram of the type of the conrodes to be fitted for the connection of the pistons to the crank shaft.

4. THE TECHNICAL MULTI-TRANSMISSION OF ENERGY FOR THE PURPOSE OF MULTIPLICATION.

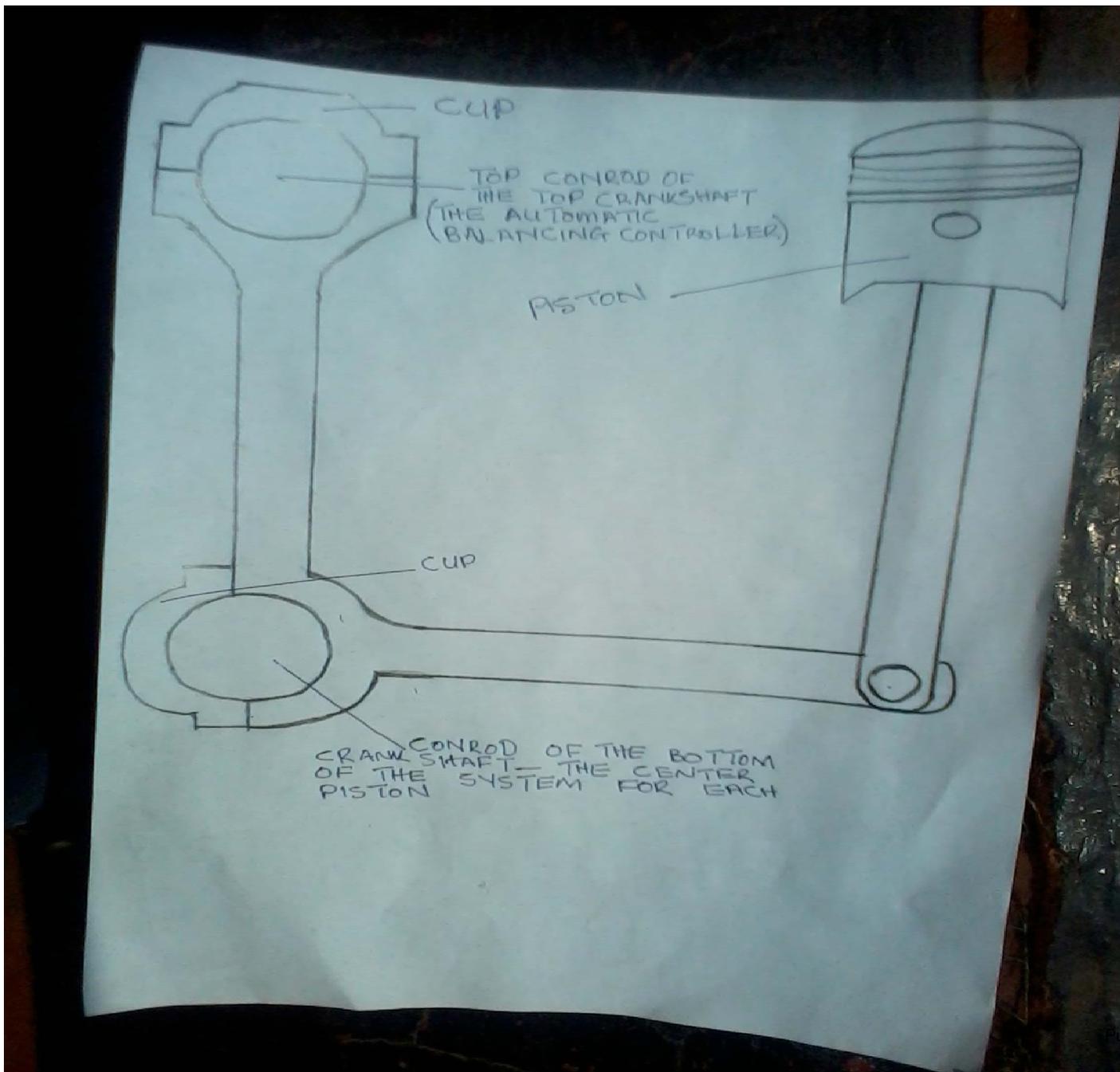
There are three stages of energy transmission and multiplication:

- a) The extension of the distances at which the pistons will be applying the energy as given in the picture XZ. As the energy will be applied at a longer distance from the centre, this is **SCIENTIFICALLY POWER TRANSMISSION AND MULTPLICATION**. There will be a variation in energy multiplication depending on the ratio at which the distances have been extended, the longer the extension the greater the multiplication of energy and vice versa.
- b) The second method of energy transmission and multiplication is in the fact that the energy applied by the pistons at a longer distance will be balancing with the top crank shaft. This is an observation that the top crank shaft will be acquiring the same energy acquired by the pistons the centres being the bottom crank shaft. Since the top crank shaft will automatically be balancing with the pistons, therefore I have named it the **AUTOMATIC BALANCING CONTROLLER**.
- c) The third method of energy transmission and multiplication is in the fact that as the energy of the pistons will be balancing with the automatic balancing controllers, the bottom crank shaft will be acquiring double and great energy.

5. Originally the engine in the picture is the 6 series but it has been theoretically converted into technical V60 and the percentages energy discovery are very high. For this reason, there is a great possibility to have absolute economy of energy, which will involve the reduction of fuel consumption by reducing the piston and cylinder volumes up to 70% so that 30% of the pistons and cylinder volumes should be used in the formulation of little energy to work in the engines. The small pistons and little energy will be able to turn the crank shaft because they will be assisted by the technical clean energy formulated within the system and the engine will have greater power than before. Similarly, the percentage of the reduction of piston volumes will be equivalent to the percentage of reduction of the greenhouse gas emissions.

I have already referred the technical V60 engine to Oak Ridge National laboratory for observation and remarks. It has been extremely a challenging research in the past 12 years to discover new engine technologies for the purpose of energy discovery and its economy for the reduction of greenhouse gas emissions while improving mechanical motion in this new millennium .

Diagram of the type of the conrodes to be fitted for the connection of the pistons to the crank shaft.



"Stop the IOM Contract to Redefine ME/CFS"

From: "Toby Vokal" [REDACTED]

Date: Wed, September 25, 2013 4:56 pm

To: pcast@ostp.gov

I am asking you to contact the Department of Health & Human Service (HHS) today and tell them to follow the lead of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) disease experts. Tell HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS.

On September 23, HHS announced that it has contracted with the IOM to develop clinical diagnostic criteria for ME/CFS, rejecting the use of criteria created by ME/CFS experts, including the 2003 Canadian Consensus Criteria (CCC). HHS pursued the contract unilaterally with virtually no if any involvement of ME/CFS experts or patients. Further, HHS has stated that it intends to use people with no expertise in ME/CFS to redefine ME/CFS. Adding to the concerns, the IOM's only other effort to define a disease has been harshly criticized by Gulf War Illness (GWI) advocates for using non-experts, emphasizing psychiatric issues over evidence of chemical injuries and moving it toward a broadly defined symptom-based syndrome. For all these reasons, ME/CFS patients have been protesting the IOM contract for weeks but HHS went ahead with the contract anyway.

Its important to note that on the same day that HHS announced that IOM would begin work, thirty-five of the leading ME/CFS researchers and clinicians wrote to Health and Human Services Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. The ME/CFS experts also urged HHS to abandon its plans to contract with the Institute of Medicine to create its own definition.

This is an unprecedented statement by our top experts and indicates researchers and clinicians are able and willing to the use the CCC now and improve on it as science develops. As the letter states, "[S]ince the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on this disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

I have been personally affected by ME/CFS. It is a debilitating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars a year in lost productivity and direct medical costs. Due to the overly broad 'case definition' (criteria) used for this disease by HHS since 1994, patients with ME/CFS are lumped together with patients with depression, deconditioning and unspecified chronic fatigue. The use of these overly broad criteria has impeded ME/CFS research and severely impaired medical care for patients like me.

Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to contact HHS today and tell them to follow the lead of ME/CFS disease experts. Tell HHS to adopt the Canadian Consensus Criteria. Tell HHS to cancel the contract with IOM.

Toby Vokal

Institute of Medicine (IOM) to begin work to develop "clinical diagnostic criteria" for ME/CFS

From: "edewit" [REDACTED]
Date: Fri, September 27, 2013 6:04 am
To: pcast@ostp.gov

I am asking you to contact the Department of Health & Human Service (HHS) today and tell them to follow the lead of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) disease experts. Tell HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS.

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Its important to note that on the same day that HHS announced that IOM would begin work, thirty-five of the leading ME/CFS researchers and clinicians wrote to Health and Human Services Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. The ME/CFS experts also urged HHS to abandon its plans to contract with the Institute of Medicine to create its own definition.

This is an unprecedented statement by our top experts and indicates researchers and clinicians are able and willing to the use the CCC now and improve on it as science develops. As the letter states, "[S]ince the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on this disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

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Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to contact HHS today and tell them to follow the lead of ME/CFS disease experts. Tell HHS to adopt the Canadian Consensus Criteria. Tell HHS to cancel the contract with IOM.

De Wit Etienne

Pls stop HHS contract with IOM re MEcfs

From: "Justin Reilly" [REDACTED]

Date: Tue, October 1, 2013 4:08 am

To: pcast@ostp.gov

Dear PCAST,

Please contact the Department of Health & Human Services (HHS) today. Tell HHS to:

Adopt the Canadian Consensus Criteria for ME/CFS and

Cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS.

On September 23, HHS announced that it had contracted the IOM to develop clinical diagnostic criteria for ME/CFS, rejecting the use of criteria created by ME/CFS experts. HHS pursued the contract unilaterally with no involvement of ME/CFS medical experts or patients. Further, HHS has stated that it intends to use people with no expertise in ME/CFS to redefine the illness. Adding to these concerns, the IOM's only other effort to define a disease – Gulf War Illness - has been harshly criticized for using non-experts, emphasizing psychiatric issues over evidence of chemical injuries, and proposing a vague definition that encompasses virtually all chronic illnesses. For all these reasons, ME/CFS patients have been protesting the IOM contract for weeks but HHS went ahead with the contract anyway.

On the same day that HHS announced that IOM would begin work, thirty-five of the leading ME/CFS researchers and clinicians responded by writing to Health and Human Services Secretary Kathleen Sebelius. The ME/CFS experts urged HHS to abandon its plans to hire the Institute of Medicine to create its own definition. They called for the Canadian Consensus Criteria (CCC), which experts have long considered to be the most accurate case definition, to be used as the sole case definition for ME/CFS.

As their letter states, “[S]ince the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on this disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable.”

I have been personally affected by ME/CFS. It is a debilitating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. The CDC estimates that over a million people in the U.S. suffer from the illness. ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars a year in lost productivity and direct medical costs. Due to the overly broad ‘case definition’ used for this disease by HHS since 1994, patients with ME/CFS are lumped together with patients with depression, deconditioning, and unspecified chronic fatigue. This broad case definition has also led to the misdiagnoses of thousands of patients with MS, incipient heart disease, and genetic disorders. The use of overly broad definitions, like the one now being developed by the IOM, has impeded ME/CFS research and held back medical care for patients like me.

Given the overwhelming opposition to HHS’ plans by both patients and experts, I am asking you to contact HHS today and tell them to follow the lead of ME/CFS disease experts.

Tell HHS to adopt the Canadian Consensus Criteria. Tell HHS to cancel the contract with IOM.

LINKS

Link to the September 23 announcement from HHS on the IOM contract. <http://bit.ly/18m7XlJ>

Link to the September 23 letter to Secretary Sebelius from the 35 ME/CFS experts
<http://bit.ly/15npS9B>

Link to additional background <http://bit.ly/16qOLY3>

Stop the IOM Contract to Redefine ME/CFS

From: "Julie Thompson" [REDACTED]
Date: Wed, October 9, 2013 8:03 am
To: pcast@ostp.gov

Dear PCAST,

Please contact the Department of Health & Human Services (HHS) **today**. Tell HHS to:

1. Adopt the Canadian Consensus Criteria for ME/CFS and
2. Cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS.

On September 23, HHS announced that it had contracted the IOM to develop clinical diagnostic criteria for ME/CFS, rejecting the use of criteria created by ME/CFS experts. HHS pursued the contract unilaterally with *no* involvement of ME/CFS medical experts or patients. Further, HHS has stated that it intends to use people with no expertise in ME/CFS to redefine the illness. Adding to these concerns, the IOM's only other effort to define a disease – Gulf War Illness - has been harshly criticized for using non-experts, emphasizing psychiatric issues over evidence of chemical injuries, and proposing a vague definition that encompasses virtually all chronic illnesses. For all these reasons, ME/CFS patients have been protesting the IOM contract for weeks but HHS went ahead with the contract anyway.

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<http://bit.ly/15npS9B>

Link to additional background <http://bit.ly/16qOLY3>

Sincerely,
Julie Thompson, RN, ARNP
disabled since 2004

Stop the IOM Contract to Redefine ME/CFS

From: "Mary Ann Kindel" [REDACTED]
Date: Mon, October 21, 2013 5:09 pm
To: pcast@ostp.gov
Cc: [REDACTED]

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS.

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

Regarding the IOM contract, the thirty-five experts stated, “[S]ince the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on this disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable.”

The use of non-experts is especially concerning because, thanks to the bad definitions that HHS has promoted, the disease is so poorly understood that the medical community at large believes the disease is either not real or is a form of depression or deconditioning. ME/CFS is not deconditioning or depression. It is a devastating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars a year in lost productivity and direct medical costs.

Given the overwhelming opposition to HHS’ plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Consensus Criteria.

For more information, see the following links or send an email to meactnow@yahoo.com.

- Link to Sept 23 announcement from HHS on the IOM contract - <http://bit.ly/18m7XIJ>
- Link to Sept 23 letter to Secretary Sebelius from the 35 ME/CFS experts - <http://bit.ly/15npS9B>
- Link to additional background - <http://bit.ly/16qOLY3>

From: "Ron Lord" [REDACTED]
Date: Mon, October 21, 2013 1:22 pm
To: pcast@ostp.gov

Please ask President Obama to order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS!

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

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The use of non-experts is especially concerning because, thanks to the bad definitions that HHS has promoted, the disease is so poorly understood that the medical community at large believes the disease is either not real or is a form of depression or deconditioning. ME/CFS is not deconditioning or depression. It is a devastating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars a year in lost productivity and direct medical costs.

Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Consensus Criteria.

For more information, see the following links or send an email to meactnow@yahoo.com.
Link to Sept 23 announcement from HHS on the IOM contract - <http://bit.ly/18m7XIJ>
Link to Sept 23 letter to Secretary Sebelius from the 35 ME/CFS experts - <http://bit.ly/15npS9B>
Link to additional background - <http://bit.ly/16qOLY3>

Sincerely,
Ron Lord

Please Resind the IOM Contract

From: "Ron Lord" [REDACTED]
Date: Mon, October 21, 2013 5:18 pm
To: pcast@ostp.gov ([more](#))
Cc: [REDACTED]

Please help us in having the HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

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Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Consensus Criteria.

Sincerely,
Ron Lord

Pls ask Obama to stop the HHS Contract with IoM for MEcfs

From: "Justin Reilly" [REDACTED]

Date: Mon, October 21, 2013 2:13 am

To: pcast@ostp.gov

I am asking you to contact one or more of the following Senators and Representatives who chair committees with jurisdiction over the Department of Health and Human Services (HHS), (Senators Harkin, Murray, Sanders; Representatives Upton, Kingston, Pitts, and Ryan (WI), on my behalf. Ask them to contact HHS today and tell Department to follow the lead of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) disease experts. Ask them to tell HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS.

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

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For more information, see the following links or send an email to meactnow@yahoo.com.

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Link to Sept 23 letter to Secretary Sebelius from the 35 ME/CFS experts - <http://bit.ly/15npS9B>

Link to additional background - <http://bit.ly/16qOLY3>

Cancel the Wasteful HHS/IOM Contract to Redefine ME/CFS

From: "Jerrold Spinhirne" [REDACTED]
Date: Mon, October 21, 2013 2:26 pm
To: pcast@ostp.gov
Cc: [REDACTED]

Dear Science Advisors,

Please order HHS to adopt the existing Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS. This expensive contract is completely unnecessary and will actually set back medical treatment of people with ME/CFS and impede progress in understanding the disease.

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

Regarding the IOM contract, the thirty-five experts stated, "[S]ince the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on this disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

The use of non-experts is especially concerning because, thanks to the bad definitions that HHS has promoted, the disease is so poorly understood that the medical community at large believes the disease is either not real or is a form of depression or deconditioning. ME/CFS is not deconditioning or depression. It is a devastating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars a year in lost productivity and direct medical costs.

Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Consensus Criteria.

For more information, see the following links or send an email to meactnow@yahoo.com

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- Link to Sept 23 letter to Secretary Sebelius from the 35 ME/CFS experts - <http://bit.ly/15npS9B>
- Link to additional background - <http://bit.ly/16qOLY3>

Sincerely,

Jerrold Spinhirne S.E.
Chicago, Illinois

An Illinois-licensed structural engineer unable to work since 1996 due to the unrecognized neurological disease myalgic encephalomyelitis, ME

Please ask the President to stop the IoM contract on MEcfs

From: "Justin Reilly" [REDACTED]

Date: Mon, October 21, 2013 4:08 am

To: pcast@ostp.gov

Please ask President Obama to order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS.

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

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Link to additional background - <http://bit.ly/16qOLY3>

Please order HHS to adopt the CCC and cancel the IOM contract to redefine ME/CFS

From: "Leela Play" [REDACTED]
Date: Mon, October 21, 2013 7:17 pm
To: pcast@ostp.gov
Cc: [REDACTED]

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

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Given the overwhelming opposition to HHS’ plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Consensus Criteria.

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What you do affects the world. I've been left to rot for 13 years. We need an expert definition for research to be relevant. We are close to getting biomarkers and effective treatment, and maybe even a cure. A bad definition would lead to the rest of my life being wasted and to dying early. Please don't let that happen.

Sincerely,

Leela Play

Tell HHS to cancel the Instituted of Medicine (IOM) contract

From: "Gabby Klein" [REDACTED]
Date: Tue, October 22, 2013 10:43 am
To: "pcast@ostp.gov" <pcast@ostp.gov>

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

On September 23, thirty-five of the leading ME/CFS researchers and clinicians [wrote](#) to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

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Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Concensus Criteria.

Gabby Klein
Flushing, NY

Tell HHS to cancel the Instituted of Medicine (IOM) contract

From: "Ron Lord" [REDACTED]
Date: Tue, October 22, 2013 9:41 am
To: pcast@ostp.gov
Cc: [REDACTED]

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

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Sincerely,
Ron Lord

Tell HHS to Cancel the Institute of Medicine (IOM) Contract

From: "David Linde" [REDACTED]

Date: Tue, October 22, 2013 9:26 am

To: pcast@ostp.gov

Cc: [REDACTED]

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

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HHS and IOM contract

From: cmsuem [REDACTED]
Date: Wed, October 23, 2013 8:52 am
To: pcast@ostp.gov

Dear President Obama,

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS.

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition.

On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

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Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Concensus Criteria.

The implications of this contract going ahead will affect all sufferers on a world-wide basis. It is of serious international concern.

Yours sincerely,
Susan Marshall
Dundee, Scotland.

RE: Dept. HHS contract with Institute of Medicine to redefine ME/CFS disease

From: "michael" [REDACTED]
Date: Wed, October 23, 2013 8:37 pm
To: "pcast@ostp.gov" <pcast@ostp.gov>

Michael S. Allen, Ph.D.
3953 18th Street
San Francisco, CA 94114
415-554-0322
Msallen1984@sbcglobal.net

I am a clinical psychologist who has been disabled for 20 years with the disease alternately known as Myalgic Encephalomyelitis (M.E.) and Chronic Fatigue Syndrome (CFS).

I have suffered from years of severe flu-like symptoms, brain damage, constant sleep deprivation, and waves of physical debilitation that can make walking to the corner seem like climbing a mountain. My symptoms wax and wane just enough that I only have what is considered a "moderate" case of M.E. There are a million people in the U.S. alone with some degree of this disease many of whom are home and or bed-bound, in constant pain.

For 20 years I've watched in despair, frustration, and anger as the NIH has ignored this epidemic disease and as the CDC has fumbled every effort it has made beginning with calling it by the trivializing name of Chronic Fatigue Syndrome.

Now, I learn the Dept. of HHS has given the Institute of Medicine (IOM) a one million dollar contract to develop new diagnostic criteria. This is wrong-headed and offensive and counter to science for so many reasons: There is already an excellent case definition developed by real experts (the IOM has no experts on this disease) known as the Canadian Consensus Criteria -- <http://www.name-us.org/DefintionsPages/DefCCC.htm>

It is pointless and a waste of time and money to ignore what is the best diagnostic criteria for M.E. yet developed. (Currently, the most widely used is the CDC's Fukuda Case Definition which is vague and emphasizes "fatigue" which is the in some ways the least important symptom.

A group of 35 recognized experts in the field of what the NIH now calls ME/CFS wrote an open letter to the Secretary of HSS urging her to endorse the Canadian Criteria and cancel the IOM contract:
<https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20Sept%202013.pdf>

That letter has been ignored. Over the 20 years I've been disabled and sick that is the usual response from the CDC and the NIH: to ignore the actual doctors and researchers who have devoted their careers to treating and understanding my disease.

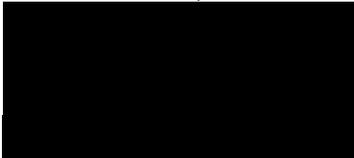
In addition, the IOM was given a similar contract to redefine Gulf War Illness, which bears great similarities to M.E. in terms of symptoms and their severity. What did the IOM do? They now call it Chronic Multi-Symptom Illness. And are recommending Cognitive Behavior Therapy (CBT) and anti-depressants. As a psychologist I can say with authority that this is absurd and medical malpractice. Imagine calling Multiple Sclerosis by that name!

I am 65 now. I was stricken in my mid 40s. I have lost my career, my life savings, and my hope to ever see a cure. I'm writing now not to ask for your help, but frankly I am begging and pleading for your help. If not for me for all the new victims of this disease, who range in age from nine years old to their 70s.

As of now, Secretary Sebelius has ignored our objections. Please help us. We are desperate.

Sincerely,

Michael S. Allen, Ph.D.



Please adopt the Canadian Consensus Criteria definition of ME/CFS

From: "Selena MKI" [REDACTED]
Date: Thu, October 24, 2013 3:36 am
To: pcast@ostp.gov
Cc: [REDACTED]

To Whom It May Concern:

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

On September 23, thirty-five of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition. On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

Regarding the IOM contract, the thirty-five experts stated, "Since the expert ME/CFS scientific and medical community had developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on the disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable.

The use of on-experts is especially concerning because, thanks to the bad definitions that HHS has promoted, the disease is so poorly understood that the medical community at large believes the disease is either not real or is a form of depression or deconditioning. ME/CFS is not deconditioning or depression. It is a devastating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars in lost productivity and direct medical costs.

Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Consensus Criteria.

Thank you for your attention to this matter.

Kind regards,

Selena
Inouye
Los Angeles, CA

Oh My Aches and Pains!
www.ohmyachesandpains.info

HHS contract with IOM

From: "Chris Heppner" [REDACTED]

Date: Mon, October 28, 2013 1:57 pm

To: pcast@ostp.gov

I write as a Canadian, but wish to contact you since the decisions made within the HHS have a powerful effect on the state here in Canada.

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

On September 23, thirty-five of the leading ME/CFS researchers and clinicians [wrote](#) to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition.

On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

Recently, another 15 of the leading ME/CFS researchers in the world added their names to the original letter, so that now nearly all the leading researchers in this field are united in expressing their intention to use the existing CCC as their working definition, and in asking HHS to cancel the IOM contract and to redirect the money to fund basic research in the disease, which has been disastrously underfunded for many years.

Regarding the IOM contract, the experts stated, "Since the expert ME/CFS scientific and medical community had developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on the disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

The use of non-experts is especially concerning because, thanks to the bad definitions that HHS has promoted in the past, the disease is so poorly understood that the medical community at large believes the disease is either not real or is a form of depression or deconditioning. ME/CFS is not deconditioning or depression. It is a devastating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars in lost productivity and direct medical costs.

Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS should cancel the

contract with IOM, and adopt the Canadian Consensus Criteria, while recognizing, as do the 50 researchers, that as more is learned that definition may need to be altered.

Sincerely, Christopher Heppner, Ph.D.

Chronic Fatigue Syndrome Issues

From: "happyarlen" [REDACTED]
Date: Wed, October 30, 2013 9:48 am
To: pcast@ostp.gov

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

On September 23, thirty-five of the leading ME/CFS researchers and clinicians [wrote](#) to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition.

On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

Regarding the IOM contract, the thirty -five experts stated, "Since the expert ME/CFS scientific and medical community had developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on the disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

The use of non-experts is especially concerning because, thanks to the bad definitions that HHS has promoted, the disease is so poorly understood that the medical community at large believes the disease is either not real or is a form of depression or deconditioning. ME/CFS is not deconditioning or depression. It is a devastating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. ME/CFS costs the U .S. economy an estimated \$17-23 billion dollars in lost productivity and direct medical costs.

Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Concensus Criteria.

ME/CFS

From: "Cheryl Gordon" [REDACTED]

Date: Sat, November 2, 2013 6:56 am

To: pcast@ostp.gov

Please order HHS to adopt the Canadian Consensus Criteria and cancel its contract with the Institute of Medicine (IOM) to redefine ME/CFS

On September 23, thirty-five of the leading ME/CFS researchers and clinicians [wrote](#) to HHS Secretary Kathleen Sebelius calling for the Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS. These experts also urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition.

On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

Regarding the IOM contract, the thirty-five experts stated, "Since the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on the disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

The use of non-experts is especially concerning because, thanks to the bad definitions that HHS has promoted, the disease is so poorly understood that the medical community at large believes the disease is either not real or is a form of depression or deconditioning. ME/CFS is not deconditioning or depression. It is a devastating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work. ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars in lost productivity and direct medical costs.

Given the overwhelming opposition to HHS' plans by both patients and experts, I am asking you to do whatever you can to get HHS to follow the lead of ME/CFS disease experts. HHS must cancel the contract with IOM. HHS must adopt the Canadian Concensus Criteria.

For US economy growth

From: "Makoto Yanase" [REDACTED]
Date: Tue, November 5, 2013 2:05 am
To: pcast@ostp.gov

This is information of huge Assets. I ask, advice to me exact contact Department or Agency. this is proposal for grow US economy . Economy is the heart of every country. Inflation or deflation, almost country countered all of the world. Every country leaders are try to find good situations. Maybe Innovation, maybe new technology, science or some country use(develop) weapon(Terrorist, cyber, missile, lobbying, chemical poison gas, Narcotics, etc). Especially, peacemaker country has more hard situations. (like USA) This is proposal for growth US economy also protect, Defense from those problems. I think solution is only one. Find huge Capital(budget), that's it. This offer is make budget for future(now).

I explain my situation. My offer is historical issue and very confidential matter. I can detect huge assets(commodities). Simple, I want to get those commodities then use for good way(under US government). Those are not private level. So I decided to contact democratic leader country.(not Communist, Muslim country). I'm Japanese man and here is Philippines. I want to request partnership(joint) with US government. This is complex and confidential proposal. Because, my offer involve huge amount of value commodities(not nature, man made) also I believe need strong back up. Those commodities are able to find(detect) only me. Because, I developed own Detector then 17 years trained detector actions. I made confidential movement. Those commodities are sure help US economy growth also innovation, science for future. But I think so hard to believe only by e-mail. I think best is talk face to face. Those commodities are not this country own(origin). Hide and historical commodities. And nobody find except me. I have existing operation, almost final now. Then I have several sites listed. Each site huge value, huge Billion to Trillion US Dollars deposited(my estimate). Problem, I have situation here, also there are time limited to contact USA. This is right information. Several countries are interested. Once other country know and get those commodities. USA will become more huge problem. Even territory, even military situations will be effect. Especially, some countries of Asia, almost corrupt Economy now. Very hungry for money. Definitely, my 1st priority is USA. Please assist or advice to me. And I'm so afraid contact this country inside. It's so risky this country. I have no time. Please response to me immediately. I attached 1 e-mail and 3 kinds of drawings(3 pages each) today. So please open then check my proposal. Please advice.

Makoto

Update: 11/18/13 - Sent same email again on November 15 with same attachments.

Attach1- (1)

RECHARGE ECONOMIC NEW ENGINE

- (1) Innovation business..... No final, continue searching.
(performance cost , kinds of risk)
- (2) Defense..... Reduce cost
(risk for USA, also relation countries)
- (3) National Security, etc....
 - (1) Terrorism
 - (2) Energy
 - (3) Climate Change
 - (4) Costs
 - (1) Medical
 - (2) Nature(Hurricane, Tornado, etc)
 - (3) Emergency , etc.
- (4) Education
- (5) **Infrastructure Development**
- (6) **Investments, Manufacturing**



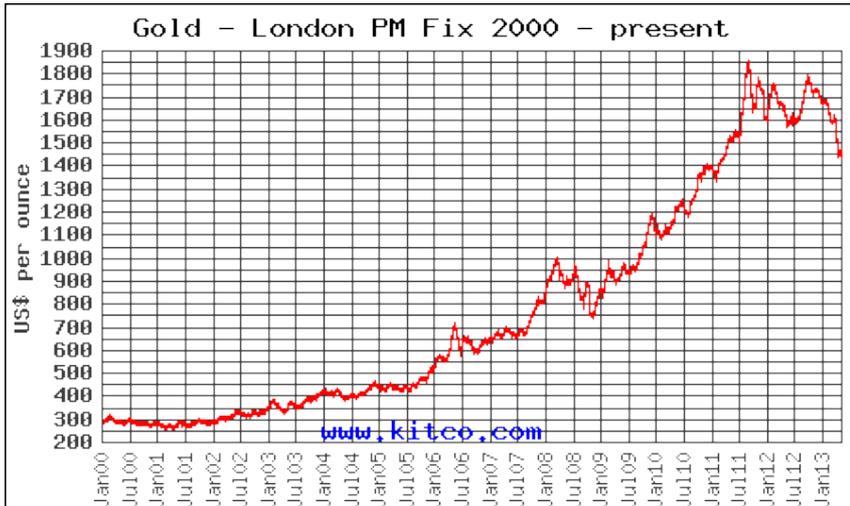
FIND CAPITAL

Natural Resources(Best thing)

Economy vs Costs

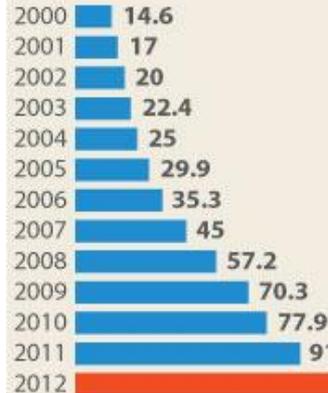
- (1) Defense
- (2) Education
- (3) Health
- (4) Social programs
- (5) others

Reduce Costs ?



Top military spenders

China's military spending (US\$ billion)



World's top military spenders, 2011 (US\$ billion)



*Based on budgeted figures. **Based on projected figures.

Source: Stockholm International Peace Research Institute

Find Most Valuable Materials

(1)GOLD value increase every year

(1) 2003 January	356.86	US\$ ounce
(2) 2008 January	889.60	US\$ ounce
(3) 2013 January	1670.95	US\$ ounce

(2)GOLD is based on Economy always.

(3)GOLD is the best materials in the world



(Proceed innovation)

OIL, Low cost → **CAPITAL** ← **GOLD**

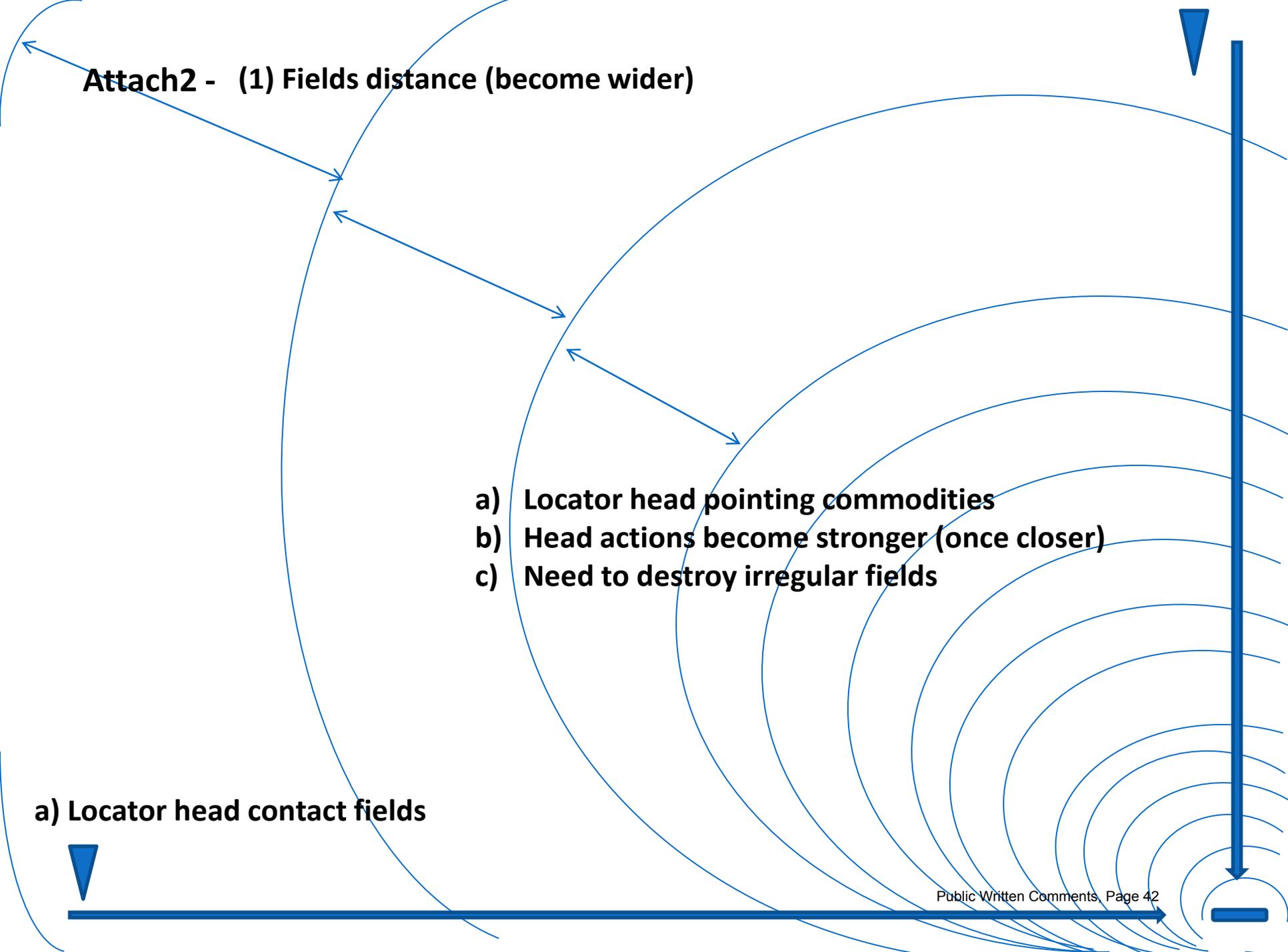


GOLD is the most Powerful Recharge New Engine

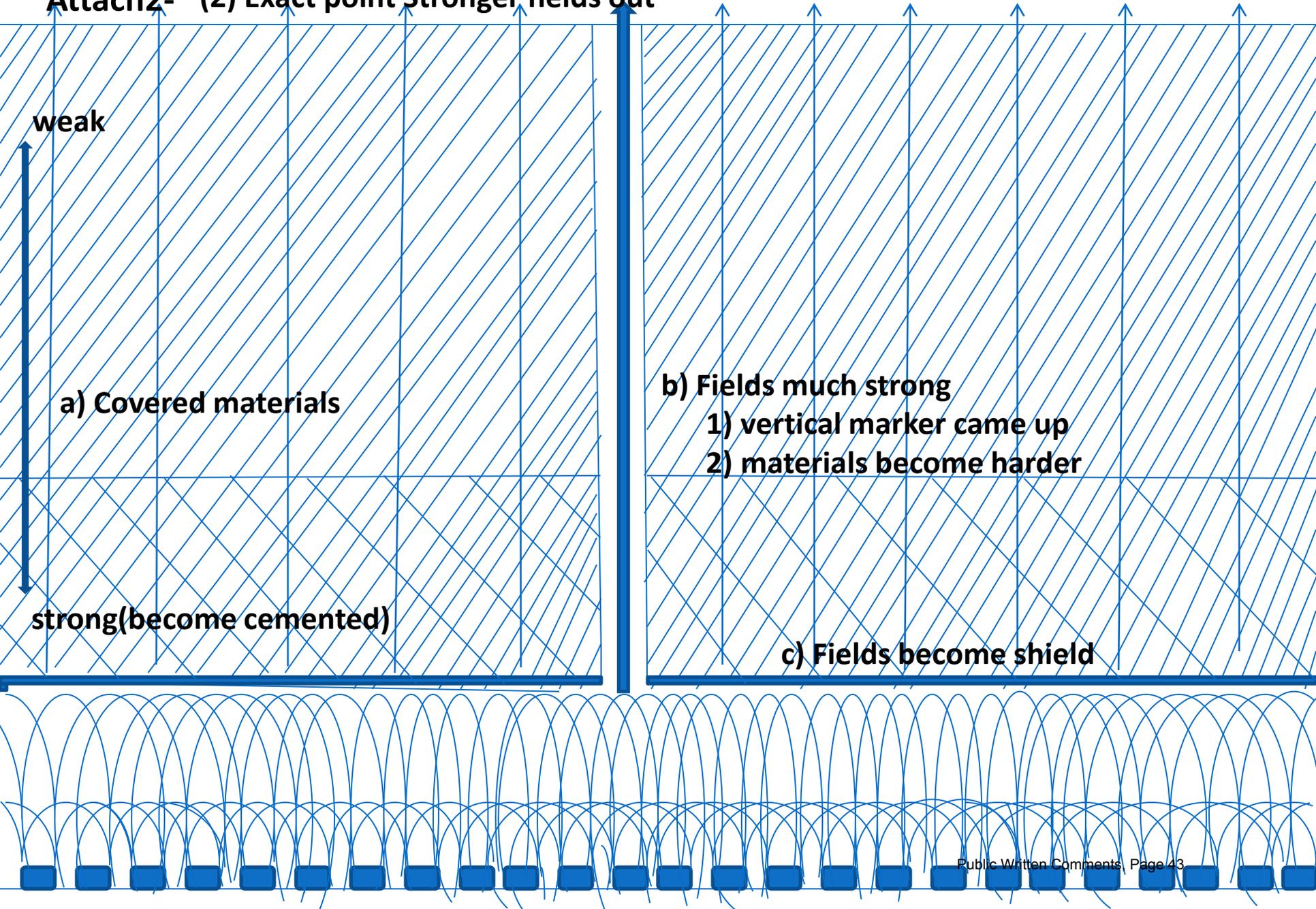
Attach2 - (1) Fields distance (become wider)

- a) Locator head pointing commodities**
- b) Head actions become stronger (once closer)**
- c) Need to destroy irregular fields**

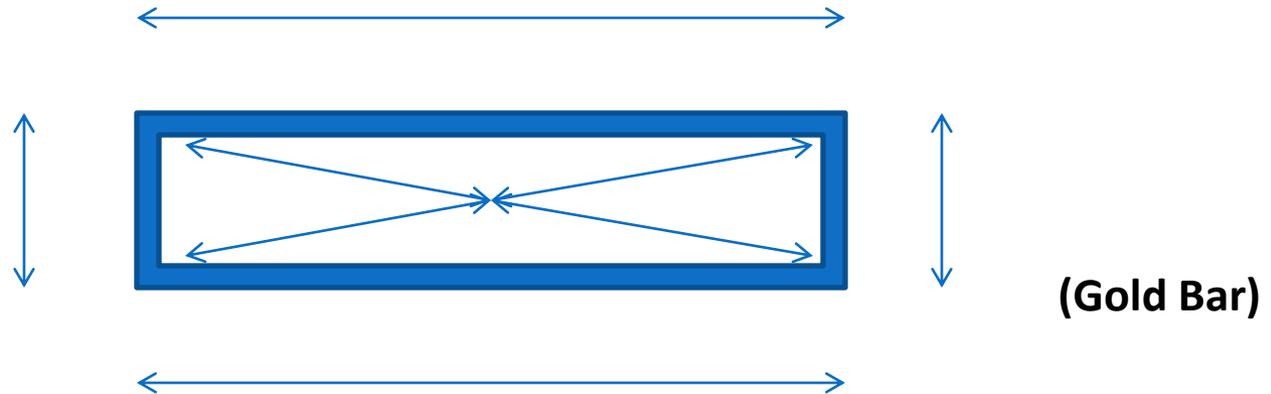
a) Locator head contact fields



Attach2- (2) Exact point Stronger fields out

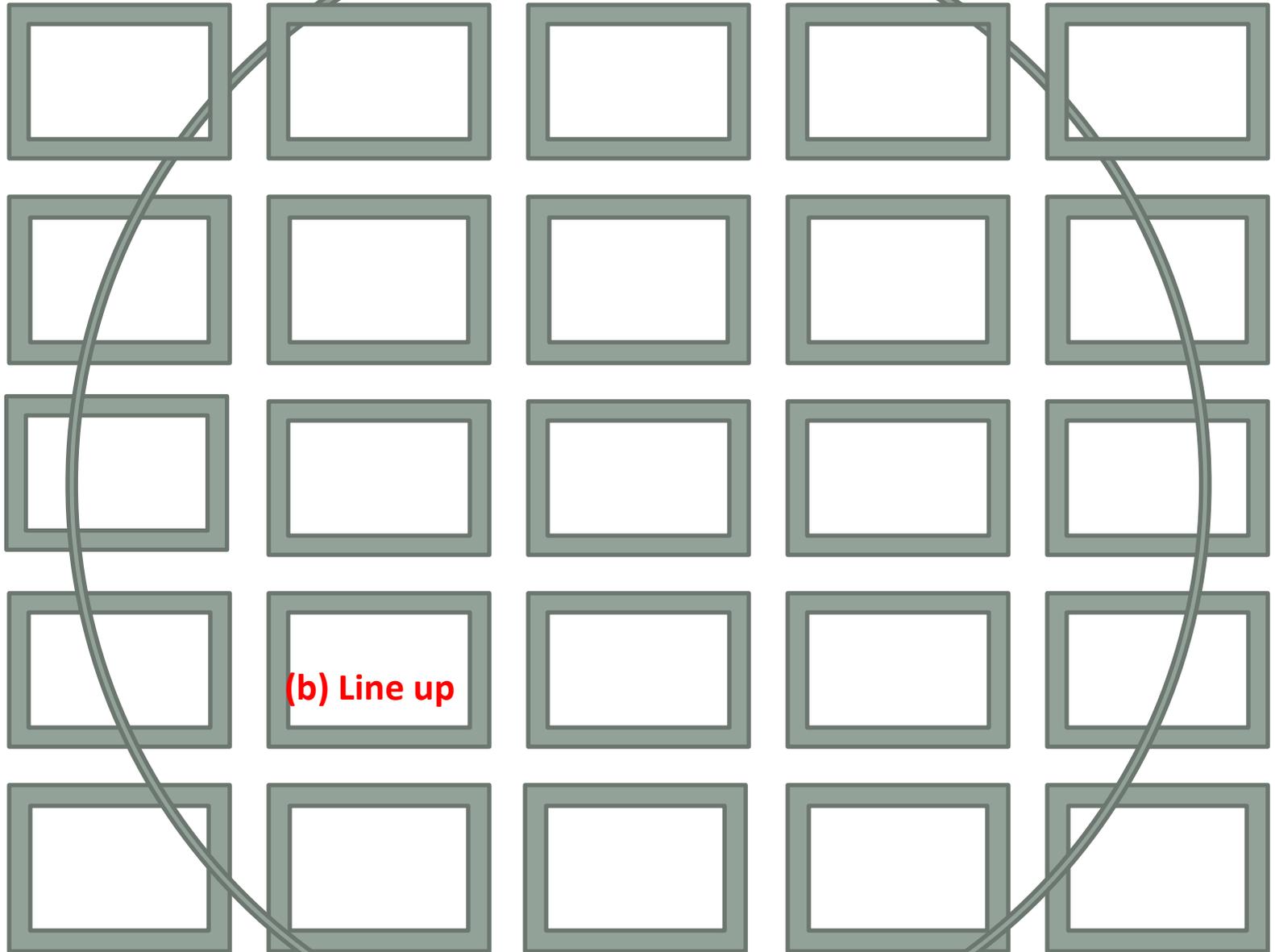


Attach2 - (3) Locator Action



- a) Head cutting size
- b) Head stop corner and center.
- c) Head actions become changing
- d) Head cutting box also line up
- e) Etc.

Attach3- (1) SITE VIEW (Operation Hole)



(c) Box

(a) Hole top



Attach3 - (2) LOCATION (SITE)

(a) Line up boxes



(b) Operation hole(existing hole)

(1) 120ft(40m) deep

(2) Final stage now

Attach3 - (3)LOCATION SITE(PICTURES)

(1)Operation house



(2)Operation hole



USA never become position NO.2 every categories. ECONOMY, MILITARY, TECHNOLOGY, SCIENCE..evrything. Only 224years, USA always NO.1. World peace depends on USA. World Economy Depends on USA. But now, balance of the world become decline. Especially, Asia some country become monster. Especially military. That's why, it's so risky reduce National budget. For my opinion, money able to buy technology, innovation. Even weapon, even scientist. So money is the base on everything. Find sure CAPITAL. That's National Security. Most important for future.

Science, maybe able to save our EARTH. Climate Change(Hurricane, Tornado), Earth Temperature up, Sea level up. Our EARTH is sick now. Which country are able to save? Peoples live in the EARTH, Sick of EARTH become heavy. Because, develop, gas, chemicals.....etc.

Science, maybe able to innovation new energy. Some of Middle East OIL producer country oil stocks bottom alreedy. Probably, hard to save that country. Maybe, become war? Someday every producer countries will be empty stocks. How to survive future of Energy? USA is NO.1 OIL consumer country in the world. Probably, new technology(Science) will be save. Innovation save future. Use budget for future of all of the world. GET CAPITAL.

This is proposal find CAPITAL for future of our EARTH, also Recharge US economic engine. I produce US government for gain US budget (science, innovation, Recharge Economy, also strong Defense).

(1)Target.....Find Most valuable materials in the world. (I'm specialist for find value commodities also special Locator developer). I detect only GOLD BARS(WW2). Those are hide materials, then only Philippines in the world. Those are hard to find this time. Every countries needs long-run economic growth and strong Defense.

(2)Attach(1)-(3) files

(1) Attach1(3pages)..... FIND SURE CAPITAL(for Recharge economic growth USA, etc)

(1)Deal my technique(know-how) for Detect commodities.

(2)Operation my existing site(final stage now)..UNDER US GOVERNMENT.

(2)Attach2(3pages).....Functions of gadget(Developed my gadget)

(1)Detect size of commodities(locator head, cutting GOLD BARS form)

(2)Detect size of box, line up(volumes).

(3)Detect many kinds of magnetic fields, then destroy many irregular fields..

(4)Pointing exact location of deposit. Etc.

(3)Attach3(3pages).....Existing operation

(1) Area Rizal province(border of Metro Manila , Philippines)

(2)Conditions.....120FT (40M) deep final stage(confidential operation)

(3)Volume.....5000 TO 10000 TONS (minimum, exactly more)

(4)Value..... 250-500 BUS\$ /AREA(MORE) (minimum)
(April10,2013... 1575 US\$/troy ounce)

(5)Verify.....Any time able to inspection. There are several area listed already. Need to discussion about that.

ONLY US GOVERNMENT.

I'm Japanese man from Philippines. This offer will be long-run growth US economy also saving for future. I want to deal partnership with US government. This is science, technical skill and abilities. I want to use my potentials and experiences. This country is Philippines. But, origin those commodities are not this country own. Story from WW2. But definitely those value are huge. Surely help long-run economy growth any country. Most important is use for good way. How can clean EARTH except budget? I trained almost 17years and find all of know-how of mechanism. I want to joint Democratic leader country. So I contact USA. Then I believe US government use for good way. I hate Communist country

also Muslim country in person. Because situation of world now. How about China, North Korea, Middle east. National Budget always increase, hard to reduce. Any countries needs budget. It's so hard to maintain clean EARTH for future. Get huge CAPITAL ,then use for future.

My situation is not easy now. So please move quickly. Please help advice or assist to me. Today, I send with attached. Please check attached ones. Please response to my e-mail, immediately.

Makoto

President Obama's promiss

From: "Els Van Hoof" [REDACTED]
Date: Sat, November 9, 2013 10:37 am
To: pcast@ostp.gov
Cc: [REDACTED]

Dear President Obama's Science Advisors,

Last year **President Obama promised publicly to Mrs Miller**, wife of Bob Miller, to have HHS look into the matter of Myalgic Encephalomyelitis (aka Chronic Fatigue Syndrome). That promise was welcomed by the entire international ME patient community, ca 1.7 mio people, and has never been forgotten.

However, in contrast to what patients were asking for, **things are totally going in the wrong direction**. The promised HHS "action" stands opposite to what patients and their clinicians/researchers need to get things finally moving forward.

HHS involved IOM (institute of medicine) to create yet another definition (and vaguer name?). Consequently,
- fatigued patients will get lumped together with neurological/immunological impaired individuals
- subgroups will have less chance to get defined and
- patients will be further away from proper treatment than ever before.

If the current plans of HHS aren't stopped in its tracks, patients will be worse off instead of better. Chances of a correct diagnosis, treatment and recovery will be even slimmer than before.

We all know this disease costs a lot of money and is a drain on economies all around the world. We also know this severe neuro-immune disease is spreading faster and faster. Sick mothers often see their teenage kids get sick as well. There is a genetic or infectious component to this disease. It will not be stopped unless science comes up with a cause or causes.

ME/CFS costs the U.S. economy an estimated \$17-23 billion dollars a year in lost productivity and direct medical costs. Lawyers, nurses, teachers, professors, ICT people, ... this disease does NOT discriminate between races, IQ, professions, ... like other severe neuro-immunological disease don't. **The entire global economy is harmed immensely by not moving science forward in the proper way: by consulting the real experts and get them funded for more research.**

Research for ME/CFS gets **LESS funding than research for male boldness**.

Patients are living in the basement of their parents' homes because of lack of income and care.

Patients are **dying a slow death**. This year the patient community lost yet again a lot of fellow patients and friends.

Patients get confined to psych wards instead of being given the proper care and treatment needed.

Patients dread going to the ER when things go very bad because of **lack of knowledge and prejudice**.

All this happens in silence. Nobody seems to care.

To get an idea of our reality of daily live, please watch the following (short) video:

<http://www.kickstarter.com/projects/959776320/canary-in-a-coal-mine>

Or Google "kickstarter" "canary in a coal mine".

If you grasp the importance and urgency of this situation, then please order the HHS to adopt the Canadian Consensus Criteria and cancel its contract with the IOM to redefine ME/CFS;

On September 23, in one unanimous voice, **35 of the leading ME/CFS researchers and clinicians wrote to HHS Secretary Kathleen Sebelius calling for the EXISTING Canadian Consensus Criteria (CCC) to be used as the sole case definition for ME/CFS.**

These experts also **urged HHS to abandon its plans to contract with the Institute of Medicine (IOM) to use non-experts to create its own definition.**

On the same day, despite an outpouring of patient opposition, HHS announced that it was going forward with the IOM contract to develop its own clinical diagnostic criteria for ME/CFS, instead of adopting the 2003 Canadian Consensus Criteria (CCC) created and endorsed by ME/CFS experts.

Regarding the IOM contract, the thirty-five experts stated:

“Since the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort (the IOM study) is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on this disease.

Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable.”

This group of experts is getting more and more support from colleagues. There are now +50 researchers/clinicians who back the request to use the CCC and stop the IOM contract.

The use of non-experts is especially concerning because, thanks to the bad definitions that HHS has promoted, the disease is so poorly understood that the medical community at large believes the disease is either not real or is a form of depression or deconditioning.

ME/CFS is not deconditioning or depression. These are proven scientific facts.

It is a devastating disease that causes neurological and immunological dysfunction and leaves patients bedridden, housebound and unable to work.

Even Dr. Ian Lipkin, the world renowned virus hunter, is now involved in the search for a cause.

Given the overwhelming opposition to HHS’ plans by both patients and experts, I am asking you to do

whatever you can to get HHS to follow the lead of ME/CFS disease experts.

HHS must cancel the contract with IOM. HHS must adopt the Canadian Consensus Criteria.

For more information, see the following links or send an email to: meactnow@yahoo.com

*) Link to Sept 23 announcement from HHS on the IOM contract: <http://bit.ly/18m7XIJ>

*) Link to Sept 23 letter to Secretary Sebelius from the 35 ME/CFS experts: <http://bit.ly/15npS9B>

*) Link to additional background: <http://bit.ly/16qOLY3>

PCAST Members, Three Conditions, and Testimony Opposing the Confirmation of Dr. France Cordova as Director of NSF

From: "Lloyd Etheredge" [REDACTED]

Date: Tue, November 12, 2013 4:55 pm

To: "Dr. John Holdren - Science Adviser to President Obama and Co-Chair, PCAST" [more](#) [REDACTED]

Cc: "Dr. Rosina Bierbaum - PCAST" [REDACTED]

Dear PCAST Co-Chairs and Colleagues:

I enclose a copy of a statement for the Senate Committee on Health, Education, Labor and Pensions concerning the nomination of Dr. France Cordova to be Director of the National Science Foundation.

Aside from constraints on Dr. Holdren, I hope that PCAST members, writing as individuals, also will oppose President Obama's nomination of Dr. Cordova in public testimony unless she is willing to make three commitments. For example, unless she is willing to make a commitment to restore the guarantee of a Scientific Merit, peer review decision at NSF, I do not believe that she can be an acceptable candidate or effective NSF Director in the eyes of the nation's scientific community.

- In the context of restoring a Scientific Merit peer review guarantee for individual grant competitions, I see no objection to a new 5% NSF Director's Fund allowing the NSF Director to make decisions about other political and societal benefits and funding such projects openly and with accountability. The NIH Director has such a fund.

Lloyd Etheredge

Dr. Lloyd S. Etheredge - Project Director
Policy Sciences Center Inc.

[The Policy Sciences Center, Inc. is a public foundation that develops and integrates knowledge and practice to advance human dignity. It was founded by Harold Lasswell, Myres McDougal, and their associates in 1948 in New Haven, CT. Further information about the Policy Sciences Center and its projects, Society, and journal is available at www.policysciences.org.]

November 11, 2013

**Statement Concerning the Nomination of France Cordova
to be Director of the National Science Foundation**

Prepared for the Senate Committee on Health, Education, Labor and Pensions

Chairman Harkin, Ranking Member Alexander and Members: My name is Lloyd Etheredge. I direct the Government Learning Project at the Policy Sciences Center, a public foundation.¹ I have worked for 30+ years to develop the science of rapid learning systems, especially rapid learning by governments. My background includes eight years of teaching research design and data analysis at MIT and serving as Director of Graduate Studies for International Relations at Yale University.

I urge you to reject the nomination of France Cordova to be Director of the National Science Foundation on three grounds.

1.) Dr. Cordova's Stewardship in a National Emergency (2008 - _____)

Dr. Cordova was appointed to the National Science Board (with accountability to oversee and provide policy guidance to the National Science Foundation) in 2008. She chairs the Committee on Strategy and Budget. NSF has a lead responsibility for basic, interdisciplinary research and transformative ideas in Economics and it administers the core grant for the advisory Committee on National Statistics of the National Research Council, a mechanism that can activate a creative, multi-disciplinary project and strategic planning. Thus, Dr. Cordova's record and candidacy should be evaluated in this light: The leading scientific models of macroeconomics failed catastrophically in 2008. The models still had sufficient truth to prevent another Great Depression but they also have proven, worldwide, to be unreliable scientific guides for rapid recovery and, repeatedly, to mislead policy makers in all countries by their forecasts and promises that their recommended policy options will be effective for a more rapid recovery. Dr. Cordova and NSF have distanced themselves from

¹ Dr. Etheredge is Director of the Government Learning and International Scientific Networks Projects at the Policy Sciences Center Inc., a public foundation created by Harold Lasswell and his associates in New Haven, CT in 1948. URL: www.policyscience.net. Dr. Etheredge can be contacted at (_____) _____

these catastrophic breakdowns and emergency scientific challenges. NSF's senior management team did what the National Science Board wanted them to do: They made themselves invisible, locked-down the NSF social, behavioral and economic sciences (SBE) Directorate, and omitted references to an economic and scientific theory crisis from their strategic plans and budget.

When the space shuttle Challenger exploded, NASA investigated both the scientific and institutional causes and redesigned the shuttle so that it would be safe for future astronauts. By contrast Dr. Cordova - who was trained in astrophysics and who has received awards from NASA - has stonewalled. I know of many letters from serious people and behind-closed-doors pleas for rapid learning and scientific leadership to improve economic ideas, models, and data systems but I am unaware of any document produced by NSF, the NSB, or Dr. Cordova's Committee on Strategy and Budget with serious discussions of breakdowns of scientific Economics. There are no rational plans for rapid learning to collect new data and restore the scientific trustworthiness of NSF-supported theory and research.² Dr. Cordova's record of stewardship is chilling.

At this point, let me address two objections that may occur to you: 1.) You may ask: "Is it fair to blame Dr. Cordova? NSF Directors, Acting Directors, and other members of the National Science Board have been silent, too. Surely the lower status people in the NSF system and many economists are more to blame. And Dr. Cordova is not an economist." My suggestion is that you address this question to Dr. Cordova: She is the person who is asking for the public's trust as the new Director of NSF.

You also might ask: 2.) "But does *anyone* know how to improve economic theory and data systems quickly?" For an answer, I suggest that you look at the spectacular rate of learning that has been achieved in this same five year period by competent and honest scientists at a well-run institution (NIH) in the field of cancer research. As the search for new cancer treatments slowed, NIH's senior leadership developed research systems to include new data, expanding to what is now

² Leading macro-economists addressed an international IMF summit earlier this year and underscored that, with current theories and data systems, they are out of good ideas to improve the rate of recovery. See Robert J. Samuelson, "The End of Macro Magic," The Washington Post, April 21, 2013. I am not aware of such honesty in National Science Board reports to Congress.

called “Everything” - all variables recorded at the genetic level. And good scientific method - adding a great many new and potentially relevant types of variables - works! Until recently, doctors diagnosed and classified cancers by the site of occurrence: now (with the help of paradigm-busting, machine learning systems that can detect patterns in Big Data systems) we know that there may be 10-15 types of tumors that appear in the breast or lung, each with a different causal pathway. Suddenly an exciting universe of new, precise treatments may be possible for cancer and, perhaps, many other diseases.³

Scientists demand integrity and competence. A rational and obvious step for any area of science (especially one as conceptually and sometimes comfortably limited as Economics) is to respond to theories that are not working by searching for missing and potentially relevant variables, building new data systems, and using analysis methods that do not limit you by your preconceptions about reality or causation.

Senators, your work as professional politicians gives you the experience to recognize that rationality is only one part of the story of human behavior. As you may recall, the discipline of economics made a mathematically convenient choice, many years ago, that seemed reasonable at the time, to base its 20th century scientific models and future national policy recommendations on limited psychological ideas and they used variables derived from accounting. However, much more of human psychology can be relevant - e.g., emotional forces, including mistrust, become much more important at times of economic crisis and breakdowns of trust.⁴ If your Committee encourages a good choice for NSF Director, many social scientists and other observant people can quickly suggest missing variables and ideas for the new, larger R&D “Everything Included” data systems that may rapidly produce upgraded, new economic theory and accelerate economic recovery.

³ Bert Vogelstein *et al.*, “Cancer Genome Landscapes,” in Science, March 29, 2013, pp. 1546 - 1558.

⁴ If there is a Kahneman “confidence trap” it is fiercely expensive, and irrelevant, for the Fed to spend billions of dollars on the unproven assumption that the current American problem of slow recovery is a “liquidity trap.” In reality, if the problems of a delayed recovery are “psychological” - as the leading economist at the IMF has suggested - there may be a cornucopia of good options..

2.) The Death of NSF's Honest Broker Role

My second, deep concern is that Dr. Cordova and her associates have overstepped their legal authority as a government agency and knowingly damaged other national institutions. They have killed the Honest Broker role of NSF's social science programs and our nation's research universities without proper notification to your Committee and without public knowledge or legal authority for this historic change.

An example is Governor Romney's claim concerning a dependency syndrome affecting 47% of Americans, undermining their motivation and a willingness to accept responsibility for one's life, and contributing to many economic and social problems. His views echo those of President Reagan. The suppressive record of NSF across the past 30+ years - despite fierce, behind-closed-doors objections within the scientific community - has been pathetic: There are no major social science textbooks with chapters addressing these Republican-believed ideas [and the textbook chapters would need to be rewritten if there were any non-zero coefficients].⁵

The National Science Board (and Dr. Cordova and her associates) were asked to rethink these embarrassing, unwritten, and illegitimate NSF restrictions again, after Governor Romney made it clear that he believed these ideas.

Most Americans, I believe, want public policies that are evidence-based and effective, and they are skeptical that ideologues and loud policy arguers on infotainment television know as much as they believe themselves to know. America deeply deserves an honest and straight-shooting NSF Director with the stature, scientific integrity, and political courage to restore an honorable Honest Broker role for NSF, to challenge aggressive and self-assured people by thoughtful evidence, and who will help to defend the political independence and civic role of our research universities.

⁵ I addressed one concern related to this problem in a letter to the Chair and Ranking Member on October 31, 2013. Discussions of other dimensions, written at different historical points and shaped by different periods of frustration, anger, sadness, and hope across 30+ years are online at www.policyscience.net

3.) NSF's Scientific Merit, Peer-Review System: Dr. Cordova and a Pending Meltdown

Senators, many members of this Committee may believe - as most of our nation's scientists still believe - that NSF operates with a guarantee of a Scientific Merit, peer-review decision similar to our jury system. [It is the traditional, trusted system used by other government scientific agencies.] However, this is a misperception and confusion created by subterfuge: Cordova *et al.* have changed the rules and expanded a new system called Merit Review that actually shifts all NSF award decisions to the government's employees (and to themselves). What they call "Merit" introduces long lists of non-Scientific Merit bases for making NSF awards - added new political and social criteria, "too hot to handle" judgments, and unknown weights that they do not fully and equally disclose in advance to all NSF applications. Nor will Cordova *et al.* disclose audited data to the scientific community showing the real reasons that the government "competitive grant" funds have been awarded or denied. Our nation's research scientists still (partly because they believe the older Scientific Merit system exists and because we believe that we "own" the research system in our fields and are responsible for it) volunteer hundreds of thousands of hours, without compensation, to evaluate about 40,000 applications/year for an NSF and National Science Board that recklessly and offensively have neutralized the older guarantees. This national system is about to melt down.

A contributing problem is money. The so-called Other Benefits rankings, undisclosed program priority weights, higher-level Program Officer decisions, NSB pressures, and other changes have been passionately advocated by lobbyists and interest groups who - behind the public facade of a Scientific Merit, peer-review system and judicial-like integrity - can achieve competitive advantages and carve up growing portions of the national science budget at a time of increased competition for funds. Program Officers are placed under duress to accommodate to these interests, while being absolved from the requirement to keep reliable, complete, and accountable public records. There are chilling rumors that - for example - Texas A&M combined insider information with an aggressive "NSF Days" campus program to secure hundreds of millions of dollars a year when its former President served as Chair of the National Science Board. And that scientific studies of racial prejudice and discrimination against Blacks (along with Honest Broker studies of Republican ideas) are being killed by a fearful and vulnerable bureaucracy.

Possibly, Dr. Cordova and her associates, by continuing to stonewall, will face down the nation's research scientists who want our Scientific Merit peer-review system restored. However, my perception is that a new NSF Director cannot govern with legitimacy unless he or she restores the guarantee of Scientific Merit, peer-review rewards.⁶ Otherwise I suspect that an alienated and quiet national meltdown is more likely. The last NSF Director resigned just ahead of a public confrontation and potential No Confidence vote by the AAAS Council, which had angrily discovered NSF's subterfuge and cancellation of traditional guarantees.⁷

Why would you entrust a major national institution to somebody with Dr. Cordova's record of the past five years? My perception is that Dr. Cordova - as an inside and consensus candidate - also lacks the independent stature and support to restore the Scientific Merit, peer-review, guarantee. She may be a candidate that is put forward by an institution that has no intention of changing. And that may be paralyzed in facing the growing self-created problem and outrage of NSF's brutally damaged and conceptually limited Economics research capability; restoring the Honest Broker role of universities in an era of mindlessness; and regaining the trust and loyalty of the nation's scientists.

Concluding Remarks: The Integrity of Democracy and a Pre-Runnymede Breakdown

In conclusion, may I also bring to your attention that Dr. Cordova and the National Science Board have shown poor (and disqualifying) judgment about our system of democratic government? Today, any individual researcher, professional society, or university President who publicly criticizes NSF faces a new top-down NSF system that has dangerously removed guarantees for anonymity,

⁶ Most scientists probably would grant the NSF Director and NSB a 5% Directors Fund for accountable spending of NSF funds for strategic projects or political benefits. NIH also has a Directors Fund.

⁷ Many of the interest groups are within the academic world. NSB beneficiaries include aggressive second- and third-tier universities where administrators now openly create "profit Centers" linked to over-charging the national science budget.

Vannevar Bush's vision for a trustworthy NSB/NSF system envisioned leadership by eminent scientists, but positions increasingly are filled by former scientists who have moved-up, permanently, to careers in academic administration. At NIH and the National Cancer Institute (by contrast) more successful and trusted leadership still is available from brilliant, eminent scientists.

removed the right to decisions based on Scientific Merit peer-review of applications, and killed the requirement for full public disclosure, and for independent audit and standards for evaluation and assured fairness and accountability by the higher bureaucracy. If I testify before this Senate Committee and publicly criticize the Chair of the National Science Board for this shift or Dr. Cordova or an Assistant Director for the SBE sciences as irresponsible fools for marginalizing, crippling, and ignoring the NSF Economics program, or for political suppression of Honest Broker evaluation of Republican ideas, or for suppressing studies of racial prejudice, any NSF Program officer will know my identity and that his/her superiors are aware of this public criticism when the Program Officer makes the new discretionary award recommendations over his/her own signatures. (Neither I *nor* the career civil service has the older protections of the Scientific Merit, peer-review system of independent, anonymous evaluation.) The honored model of independent, peer juries and our system of justice, used to design the original NSF system, has been degraded by Cordova *et al.* to a national pre-Runnymede system. The new national scientific management system - crafted by very bad judgment - places everyone under duress and, with a chilling effect, undermines the integrity and freedom of our democratic system. Specifically, it risks a suppressive bias in public testimony and criticisms of NSF and of Dr. Cordova's current candidacy received by your Committee.

How much of a current problem is this duress and bias? At the moment, I suspect that it is small because the dust cloud that has obscured the pre-Runnymede changes in trusted power relationships is just beginning to dissipate. However the dangerous, chilling effects and inhibitions are likely to grow. You should defend the integrity of our democratic political process and appoint an NSF Director with the stature and independence to cancel the power grab and restore the Scientific Merit, independent peer review guarantee. Dr. Cordova is not a candidate who meets these requirements.

Thank you.

Attachment A: Bert Vogelstein *et al.*, "Cancer Genome Landscapes," Science, March 29, 2013, pp. 1546 - 1558.

REVIEW

Cancer Genome Landscapes

Bert Vogelstein, Nickolas Papadopoulos, Victor E. Velculescu, Shibin Zhou, Luis A. Diaz Jr., Kenneth W. Kinzler*

Over the past decade, comprehensive sequencing efforts have revealed the genomic landscapes of common forms of human cancer. For most cancer types, this landscape consists of a small number of “mountains” (genes altered in a high percentage of tumors) and a much larger number of “hills” (genes altered infrequently). To date, these studies have revealed ~140 genes that, when altered by intragenic mutations, can promote or “drive” tumorigenesis. A typical tumor contains two to eight of these “driver gene” mutations; the remaining mutations are passengers that confer no selective growth advantage. Driver genes can be classified into 12 signaling pathways that regulate three core cellular processes: cell fate, cell survival, and genome maintenance. A better understanding of these pathways is one of the most pressing needs in basic cancer research. Even now, however, our knowledge of cancer genomes is sufficient to guide the development of more effective approaches for reducing cancer morbidity and mortality.

Ten years ago, the idea that all of the genes altered in cancer could be identified at base-pair resolution would have seemed like science fiction. Today, such genome-wide analysis, through sequencing of the exome (see Box 1, Glossary, for definitions of terms used in this Review) or of the whole genome, is routine.

The prototypical exomic studies of cancer evaluated ~20 tumors at a cost of >\$100,000 per case (1–3). Today, the cost of this sequencing has been reduced 100-fold, and studies reporting the sequencing of more than 100 tumors of a given type are the norm (table S1A). Although vast amounts of data can now be readily obtained, deciphering this information in meaningful terms is still challenging. Here, we review what has been learned about cancer genomes from these sequencing studies—and, more importantly, what this information has taught us about cancer biology and future cancer management strategies.

How Many Genes Are Subtly Mutated in a Typical Human Cancer?

In common solid tumors such as those derived from the colon, breast, brain, or pancreas, an average of 33 to 66 genes display subtle somatic mutations that would be expected to alter their protein products (Fig. 1A). About 95% of these mutations are single-base substitutions (such as C>G), whereas the remainder are deletions or insertions of one or a few bases (such as CTT>CT) (table S1B). Of the base substitutions, 90.7% result in missense changes, 7.6% result in nonsense changes, and 1.7% result in alterations of splice sites or untranslated regions immediately adjacent to the start and stop codons (table S1B).

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Certain tumor types display many more or many fewer mutations than average (Fig. 1B). Notable among these outliers are melanomas and lung tumors, which contain ~200 nonsynonymous mutations per tumor (table S1C). These larger numbers reflect the involvement of potent mutagens (ultraviolet light and cigarette smoke, respectively) in the pathogenesis of these tumor types. Accordingly, lung cancers from smokers have 10 times as many somatic mutations as those from nonsmokers (4). Tumors with defects in DNA repair form another group of outliers (5). For example, tumors with mismatch repair defects can harbor thousands of mutations (Fig. 1B), even more than lung tumors or melanomas. Recent studies have shown that high numbers of mutations are also found in tumors with genetic alterations of the proofreading domain of DNA polymerases POLE or POLD1 (6, 7). At the other end of the spectrum, pediatric tumors and leukemias harbor far fewer point mutations: on average, 9.6 per tumor (table S1C). The basis for this observation is considered below.

Mutation Timing

When do these mutations occur? Tumors evolve from benign to malignant lesions by acquiring a series of mutations over time, a process that has been particularly well studied in colorectal tumors (8, 9). The first, or “gatekeeping,” mutation provides a selective growth advantage to a normal epithelial cell, allowing it to outgrow the cells that surround it and become a microscopic clone (Fig. 2). Gatekeeping mutations in the colon most often occur in the *APC* gene (10). The small adenoma that results from this mutation grows slowly, but a second mutation in another gene, such as *KRAS*, unleashes a second round of clonal growth that allows an expansion of cell number (9). The cells with only the *APC* mutation may persist, but their cell numbers are small compared with the cells that

have mutations in both genes. This process of mutation followed by clonal expansion continues, with mutations in genes such as *PIK3CA*, *SMAD4*, and *TP53*, eventually generating a malignant tumor that can invade through the underlying basement membrane and metastasize to lymph nodes and distant organs such as the liver (11). The mutations that confer a selective growth advantage to the tumor cell are called “driver” mutations. It has been estimated (12) that each driver mutation provides only a small selective growth advantage to the cell, on the order of a 0.4% increase in the difference between cell birth and cell death. Over many years, however, this slight increase, compounded once or twice per week, can result in a large mass, containing billions of cells.

The number of mutations in certain tumors of self-renewing tissues is directly correlated with age (13). When evaluated through linear regression, this correlation implies that more than half of the somatic mutations identified in these tumors occur during the preneoplastic phase; that is, during the growth of normal cells that continuously replenish gastrointestinal and genitourinary epithelium and other tissues. All of these pre-neoplastic mutations are “passenger” mutations that have no effect on the neoplastic process. This result explains why a colorectal tumor in a 90-year-old patient has nearly twice as many mutations as a morphologically identical colorectal tumor in a 45-year-old patient. This finding also partly explains why advanced brain tumors (glioblastomas) and pancreatic cancers (pancreatic ductal adenocarcinomas) have fewer mutations than colorectal tumors; glial cells of the brain and epithelial cells of the pancreatic ducts do not replicate, unlike the epithelial cells lining the crypts of the colon. Therefore, the gatekeeping mutation in a pancreatic or brain cancer is predicted to occur in a precursor cell that contains many fewer mutations than are present in a colorectal precursor cell. This line of reasoning also helps to explain why pediatric cancers have fewer mutations than adult tumors. Pediatric cancers often occur in non-self-renewing tissues, and those that arise in renewing tissues (such as leukemias) originate from precursor cells that have not renewed themselves as often as in adults. In addition, pediatric tumors, as well as adult leukemias and lymphomas, may require fewer rounds of clonal expansion than adult solid tumors (8, 14). Genome sequencing studies of leukemia patients support the idea that mutations occur as random events in normal precursor cells before these cells acquire an initiating mutation (15).

When during tumorigenesis do the remaining somatic mutations occur? Because mutations in tumors occur at predictable and calculable rates (see below), the number of somatic mutations in tumors provides a clock, much like the clock used in evolutionary biology to determine species

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divergence time. The number of mutations has been measured in tumors representing progressive stages of colorectal and pancreatic cancers (11, 16). Applying the evolutionary clock model to these data leads to two unambiguous conclusions: First, it takes decades to develop a full-blown, metastatic cancer. Second, virtually all of the mutations in metastatic lesions were already present in a large number of cells in the primary tumors.

The timing of mutations is relevant to our understanding of metastasis, which is responsible for the death of most patients with cancer. The primary tumor can be surgically removed, but the residual metastatic lesions—often undetectable and widespread—remain and eventually enlarge, compromising the function of the lungs, liver, or other organs. From a genetics perspective, it would seem that there must be mutations that convert a primary cancer to a metastatic one, just as there are mutations that convert a normal cell to a benign tumor, or a benign tumor to a malignant one (Fig. 2). Despite intensive effort, however, consistent genetic alterations that distinguish cancers that metastasize from cancers that have not yet metastasized remain to be identified.

One potential explanation invokes mutations or epigenetic changes that are difficult to identify with current technologies (see section on “dark matter” below). Another explanation is that metastatic lesions have not yet been studied in sufficient detail to identify these genetic alterations, particularly if the mutations are heterogeneous in nature. But another possible explanation is that there are no metastasis genes. A malignant primary tumor can take many years to metastasize, but this process is, in principle, explicable by stochastic processes alone (17, 18). Advanced tumors release millions of cells into the circulation each day, but these cells have short half-lives, and only a minuscule fraction establish metastatic lesions (19). Conceivably, these circulating cells may, in a nondeterministic manner, infrequently and randomly lodge in a capillary bed in an organ that provides a favorable microenvironment for growth. The bigger the primary tumor mass, the more likely that this process will occur. In this scenario, the continual evolution of the primary tumor would reflect local selective advantages rather than future selective advantages. The idea that growth at metastatic sites is not dependent on additional genetic alterations is also supported by recent results showing that even normal cells, when placed in suitable environments such as lymph nodes, can grow into organoids, complete with a functioning vasculature (20).

Other Types of Genetic Alterations in Tumors

Though the rate of point mutations in tumors is similar to that of normal cells, the rate of chromosomal changes in cancer is elevated (21). Therefore, most solid tumors display widespread changes in chromosome number (aneuploidy), as well as deletions, inversions, translocations,

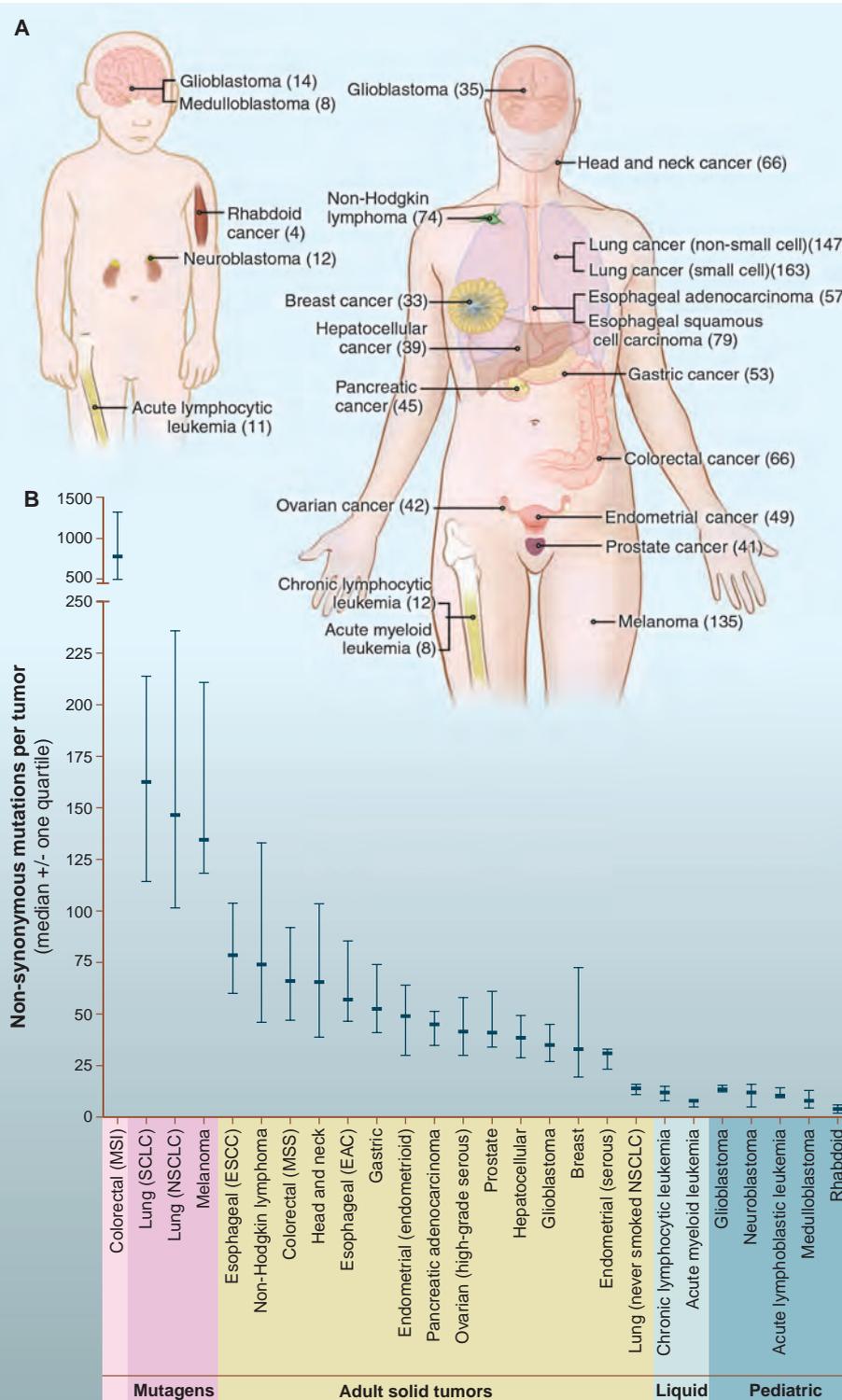


Fig. 1. Number of somatic mutations in representative human cancers, detected by genome-wide sequencing studies. (A) The genomes of a diverse group of adult (right) and pediatric (left) cancers have been analyzed. Numbers in parentheses indicate the median number of nonsynonymous mutations per tumor. **(B)** The median number of nonsynonymous mutations per tumor in a variety of tumor types. Horizontal bars indicate the 25 and 75% quartiles. MSI, microsatellite instability; SCLC, small cell lung cancers; NSCLC, non-small cell lung cancers; ESCC, esophageal squamous cell carcinomas; MSS, microsatellite stable; EAC, esophageal adenocarcinomas. The published data on which this figure is based are provided in table S1C.

CREDIT: FIG. 1A, I.E. COOK

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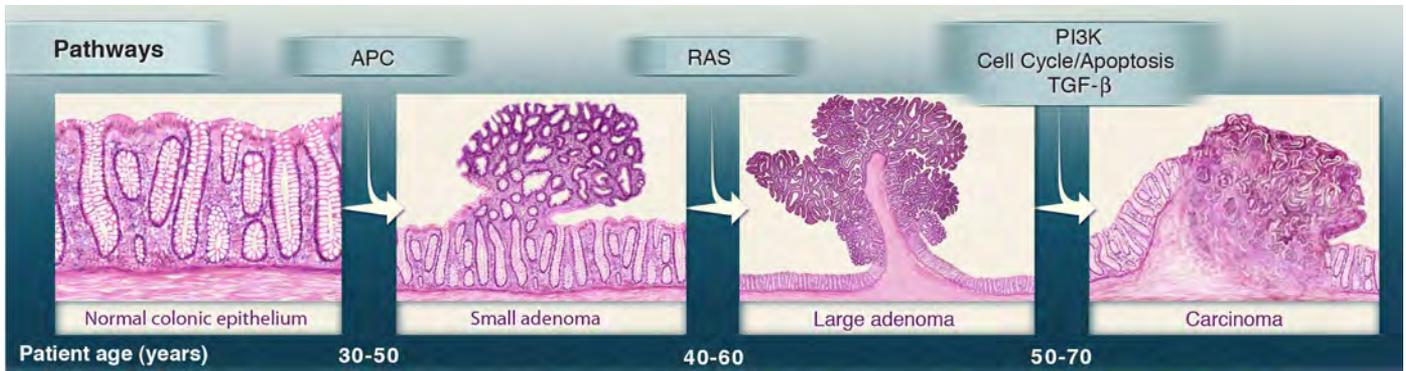


Fig. 2. Genetic alterations and the progression of colorectal cancer. The major signaling pathways that drive tumorigenesis are shown at the transitions between each tumor stage. One of several driver genes that encode compo-

ponents of these pathways can be altered in any individual tumor. Patient age indicates the time intervals during which the driver genes are usually mutated. Note that this model may not apply to all tumor types. TGF- β , transforming growth factor- β .

and other genetic abnormalities. When a large part of a chromosome is duplicated or deleted, it is difficult to identify the specific “target” gene(s) on the chromosome whose gain or loss confers a growth advantage to the tumor cell. Target genes are more easily identified in the case of chromosome translocations, homozygous deletions, and gene amplifications. Translocations generally fuse two genes to create an oncogene (such as *BCR-ABL* in chronic myelogenous leukemia) but, in a small number of cases, can inactivate a tumor suppressor gene by truncating it or separating it from its promoter. Homozygous deletions often involve just one or a few genes, and the target is always a tumor suppressor gene. Amplifications contain an oncogene whose protein product is abnormally active simply because the tumor cell contains 10 to 100 copies of the gene per cell, compared with the two copies present in normal cells.

Most solid tumors have dozens of translocations; however, as with point mutations, the majority of translocations appear to be passengers rather than drivers. The breakpoints of the translocations are often in “gene deserts” devoid of known genes, and many of the translocations and homozygous deletions are adjacent to fragile sites that are prone to breakage. Cancer cells can, perhaps, survive such chromosome breaks more easily than normal cells because they contain mutations that incapacitate genes like *TP53*, which would normally respond to DNA damage by triggering cell death. Studies to date indicate that there are roughly 10 times fewer genes affected by chromosomal changes than by point mutations. Figure 3 shows the types and distribution of genetic alterations that affect protein-coding genes in five representative tumor types. Protein-coding genes account for only ~1.5% of the total genome, and the number of alterations in noncoding regions is proportionately higher than the number affecting coding regions. The vast majority of the alterations in noncoding regions are presumably passengers. These noncoding

mutations, as well as the numerous epigenetic changes found in cancers, will be discussed later.

Drivers Versus Passenger Mutations

Though it is easy to define a “driver gene mutation” in physiologic terms (as one conferring a selective growth advantage), it is more difficult to identify which somatic mutations are drivers and which are passengers. Moreover, it is important to point out that there is a fundamental difference between a driver gene and a driver gene mutation. A driver gene is one that contains driver gene mutations. But driver genes may also contain passenger gene mutations. For example, *APC* is a large driver gene, but only

those mutations that truncate the encoded protein within its N-terminal 1600 amino acids are driver gene mutations. Missense mutations throughout the gene, as well as protein-truncating mutations in the C-terminal 1200 amino acids, are passenger gene mutations.

Numerous statistical methods to identify driver genes have been described. Some are based on the frequency of mutations in an individual gene compared with the mutation frequency of other genes in the same or related tumors after correction for sequence context and gene size (22, 23). Other methods are based on the predicted effects of mutation on the encoded protein, as inferred from biophysical studies (24–26). All of these methods are useful for prioritizing genes that are most likely to promote a selective growth advantage when mutated. When the number of mutations in a gene is very high, as with *TP53* or *KRAS*, any reasonable statistic will indicate that the gene is extremely likely to be a driver gene. These highly mutated genes have been termed “mountains” (1). Unfortunately, however, genes with more than one, but still relatively few mutations (so called “hills”) numerically dominate cancer genome landscapes (1). In these cases, methods based on mutation frequency and context alone cannot reliably indicate which genes are drivers, because the background rates of mutation vary so much among different patients and regions of the genome. Recent studies of normal cells have indicated that the rate of mutation varies by more than 100-fold within the genome (27). In tumor cells, this variation can be higher and may affect whole

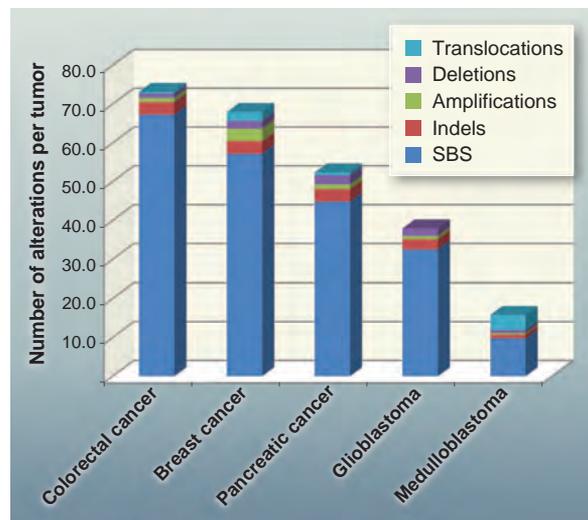


Fig. 3. Total alterations affecting protein-coding genes in selected tumors. Average number and types of genomic alterations per tumor, including single-base substitutions (SBS), small insertions and deletions (indels), amplifications, and homozygous deletions, as determined by genome-wide sequencing studies. For colorectal, breast, and pancreatic ductal cancer, and medulloblastomas, translocations are also included. The published data on which this figure is based are provided in table S1D.

Box 1. Glossary

Adenoma: A benign tumor composed of epithelial cells.

Alternative lengthening of telomeres (ALT): A process of maintaining telomeres independent of telomerase, the enzyme normally responsible for telomere replication.

Amplification: A genetic alteration producing a large number of copies of a small segment (less than a few megabases) of the genome.

Angiogenesis: the process of forming vascular conduits, including veins, arteries, and lymphatics.

Benign tumor: An abnormal proliferation of cells driven by at least one mutation in an oncogene or tumor suppressor gene. These cells are not invasive (i.e., they cannot penetrate the basement membrane lining them), which distinguishes them from malignant cells.

Carcinoma: A type of malignant tumor composed of epithelial cells.

Clonal mutation: A mutation that exists in the vast majority of the neoplastic cells within a tumor.

Driver gene mutation (driver): A mutation that directly or indirectly confers a selective growth advantage to the cell in which it occurs.

Driver gene: A gene that contains driver gene mutations (Mut-Driver gene) or is expressed aberrantly in a fashion that confers a selective growth advantage (Epi-Driver gene).

Epi-driver gene: A gene that is expressed aberrantly in cancers in a fashion that confers a selective growth advantage.

Epigenetic: Changes in gene expression or cellular phenotype caused by mechanisms other than changes in the DNA sequence.

Exome: The collection of exons in the human genome. Exome sequencing generally refers to the collection of exons that encode proteins.

Gatekeeper: A gene that, when mutated, initiates tumorigenesis. Examples include *RB*, mutations of which initiate retinoblastomas, and *VHL*, whose mutations initiate renal cell carcinomas.

Germline genome: An individual's genome, as inherited from their parents.

Germline variants: Variations in sequences observed in different individuals. Two randomly chosen individuals differ by ~20,000 genetic variations distributed throughout the exome.

Human leukocyte antigen (HLA): A protein encoded by genes that determine an individual's capacity to respond to specific antigens or reject transplants from other individuals.

Homozygous deletion: Deletion of both copies of a gene segment (the one inherited from the mother, as well as that inherited from the father).

Indel: A mutation due to small insertion or deletion of one or a few nucleotides.

Karyotype: Display of the chromosomes of a cell on a microscopic slide, used to evaluate changes in chromosome number as well as structural alterations of chromosomes.

Kinase: A protein that catalyzes the addition of phosphate groups to other molecules, such as proteins or lipids. These proteins are essential to nearly all signal transduction pathways.

Liquid tumors: Tumors composed of hematopoietic (blood) cells, such as leukemias. Though lymphomas generally form solid masses in lymph nodes, they are often classified as liquid tumors because of their derivation from hematopoietic cells and ability to travel through lymphatics.

Malignant tumor: An abnormal proliferation of cells driven by mutations in oncogenes or tumor suppressor genes that has already invaded their surrounding stroma. It is impossible to distinguish an isolated benign tumor cell from an isolated malignant tumor cell. This distinction can be made only through examination of tissue architecture.

Metastatic tumor: A malignant tumor that has migrated away from its primary site, such as to draining lymph nodes or another organ.

Methylation: Covalent addition of a methyl group to a protein, DNA, or other molecule.

Missense mutation: A single-nucleotide substitution (e.g., C to T) that results in an amino acid substitution (e.g., histidine to arginine).

Mut-driver gene: A gene that contains driver gene mutations.

Nonsense mutation: A single-nucleotide substitution (e.g., C to T) that results in the production of a stop codon.

Nonsynonymous mutation: A mutation that alters the encoded amino acid sequence of a protein. These include missense, nonsense, splice site, translation start, translation stop, and indel mutations.

Oncogene: A gene that, when activated by mutation, increases the selective growth advantage of the cell in which it resides.

Passenger mutation (passenger): A mutation that has no direct or indirect effect on the selective growth advantage of the cell in which it occurred.

Primary tumor: The original tumor at the site where tumor growth was initiated. This can be defined for solid tumors, but not for liquid tumors.

Promoter: A region within or near the gene that helps regulate its expression.

Rearrangement: A mutation that juxtaposes nucleotides that are normally separated, such as those on two different chromosomes.

Selective growth advantage (*s*): The difference between birth and death in a cell population. In normal adult cells in the absence of injury, $s = 0.000000$.

Self-renewing tissues: Tissues whose cells normally repopulate themselves, such as those lining the gastrointestinal or urogenital tracts, as well as blood cells.

Single-base substitution (SBS): A single-nucleotide substitution (e.g., C to T) relative to a reference sequence or, in the case of somatic mutations, relative to the germline genome of the person with a tumor.

Solid tumors: Tumors that form discrete masses, such as carcinomas or sarcomas.

Somatic mutations: Mutations that occur in any non-germ cell of the body after conception, such as those that initiate tumorigenesis.

Splice sites: Small regions of genes that are juxtaposed to the exons and direct exon splicing.

Stem cell: An immortal cell that can repopulate a particular cell type.

Subclonal mutation: A mutation that exists in only a subset of the neoplastic cells within a tumor.

Translocation: A specific type of rearrangement where regions from two nonhomologous chromosomes are joined.

Tumor suppressor gene: A gene that, when inactivated by mutation, increases the selective growth advantage of the cell in which it resides.

Untranslated regions: Regions within the exons at the 5' and 3' ends of the gene that do not encode amino acids.

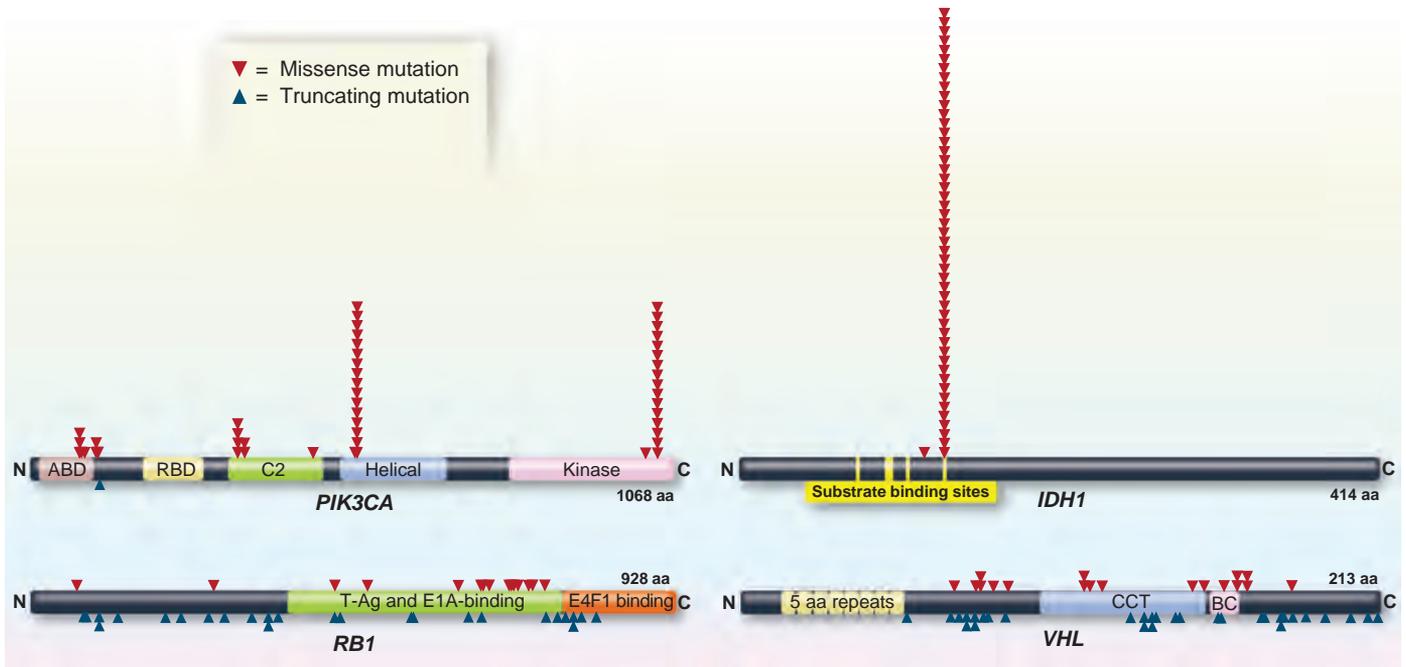


Fig. 4. Distribution of mutations in two oncogenes (*PIK3CA* and *IDH1*) and two tumor suppressor genes (*RB1* and *VHL*). The distribution of missense mutations (red arrowheads) and truncating mutations (blue arrowheads) in representative oncogenes and tumor suppressor genes are shown. The data were

collected from genome-wide studies annotated in the COSMIC database (release version 61). For *PIK3CA* and *IDH1*, mutations obtained from the COSMIC database were randomized by the Excel RAND function, and the first 50 are shown. For *RB1* and *VHL*, all mutations recorded in COSMIC are plotted. aa, amino acids.

regions of the genome in an apparently random fashion (28). Thus, at best, methods based on mutation frequency can only prioritize genes for further analysis but cannot unambiguously identify driver genes that are mutated at relatively low frequencies.

Further complicating matters, there are two distinct meanings of the term “driver gene” that are used in the cancer literature. The driver-versus-passenger concept was originally used to distinguish mutations that caused a selective growth advantage from those that did not (29). According to this definition, a gene that does not harbor driver gene mutations cannot be a driver gene. But many genes that contain few or no driver gene mutations have been labeled driver genes in the literature. These include genes that are overexpressed, underexpressed, or epigenetically altered in tumors, or those that enhance or inhibit some aspect of tumorigenicity when their expression is experimentally manipulated. Though a subset of these genes may indeed play an important role in the neoplastic process, it is confusing to lump them all together as driver genes.

To reconcile the two connotations of driver genes, we suggest that genes suspected of increasing the selective growth advantage of tumor cells be categorized as either “Mut-driver genes” or “Epi-driver genes.” Mut-driver genes contain a sufficient number or type of driver gene mutations to unambiguously distinguish them from other genes. Epi-driver genes are expressed aber-

rantly in tumors but not frequently mutated; they are altered through changes in DNA methylation or chromatin modification that persist as the tumor cell divides.

A Ratiometric Method to Identify and Classify Mut-Driven Genes

If mutation frequency, corrected for mutation context, gene length, and other parameters, cannot reliably identify modestly mutated driver genes, what can? In our experience, the best way to identify Mut-driver genes is through their pattern of mutation rather than through their mutation frequency. The patterns of mutations in well-studied oncogenes and tumor suppressor genes are highly characteristic and nonrandom. Oncogenes are recurrently mutated at the same amino acid positions, whereas tumor suppressor genes are mutated through protein-truncating alterations throughout their length (Fig. 4 and table S2A).

On the basis of these mutation patterns rather than frequencies, we can determine which of the 18,306 mutated genes containing a total of 404,863 subtle mutations that have been recorded in the Catalogue of Somatic Mutations in Cancer (COSMIC) database (30) are Mut-driver genes and whether they are likely to function as oncogenes or tumor suppressor genes. To be classified as an oncogene, we simply require that >20% of the recorded mutations in the gene are at recurrent positions and are missense (see legend to table S2A). To be classified as a tumor suppressor

gene, we analogously require that >20% of the recorded mutations in the gene are inactivating. This “20/20 rule” is lenient in that all well-documented cancer genes far surpass these criteria (table S2A).

The following examples illustrate the value of the 20/20 rule. When *IDH1* mutations were first identified in brain tumors, their role in tumorigenesis was unknown (2, 31). Initial functional studies suggested that *IDH1* was a tumor suppressor gene and that mutations inactivated this gene (32). However, nearly all of the mutations in *IDH1* were at the identical amino acid, codon 132 (Fig. 4). As assessed by the 20/20 rule, this distribution unambiguously indicated that *IDH1* was an oncogene rather than a tumor suppressor gene, and this conclusion was eventually supported by biochemical experiments (33, 34). Another example is provided by mutations in *NOTCH1*. In this case, some functional studies suggested that *NOTCH1* was an oncogene, whereas others suggested it was a tumor suppressor gene (35, 36). The situation could be clarified through the application of the 20/20 rule to *NOTCH1* mutations in cancers. In “liquid tumors” such as lymphomas and leukemias, the mutations were often recurrent and did not truncate the predicted protein (37). In squamous cell carcinomas, the mutations were not recurrent and were usually inactivating (38–40). Thus, the genetic data clearly indicated that *NOTCH1* functions differently in different tumor types. The idea that the same gene can function

in completely opposite ways in different cell types is important for understanding cell signaling pathways.

How Many Mut-Driver Genes Exist?

Though all 20,000 protein-coding genes have been evaluated in the genome-wide sequencing studies of 3284 tumors, with a total of 294,881 mutations reported, only 125 Mut-driver genes, as defined by the 20/20 rule, have been discovered to date (table S2A). Of these, 71 are tumor suppressor genes and 54 are oncogenes. An important but relatively small fraction (29%) of these genes was discovered to be mutated through unbiased genome-wide sequencing; most of these genes had already been identified by previous, more directed investigations.

How many more Mut-driver genes are yet to be discovered? We believe that a plateau is being reached, because the same Mut-driver genes keep being “rediscovered” in different tumor types. For example, *MLL2* and *MLL3* mutations were originally discovered in medulloblastomas (41) and were subsequently discovered to be mutated in non-Hodgkin lymphomas, prostate cancers, breast cancers, and other tumor types (42–45). Similarly, *ARID1A* mutations were first discovered to be mutated in clear-cell ovarian cancers (46, 47) and were subsequently shown to be mutated in tumors of several other organs, including those of the stomach and liver (48–50). In recent studies of several types of lung cancer (4, 51, 52), nearly all genes found to be mutated at significant

frequencies had already been identified in tumors of other organs. In other words, the number of frequently altered Mut-driver genes (mountains) is nearing saturation. More mountains will undoubtedly be discovered, but these will likely be in uncommon tumor types that have not yet been studied in depth.

The newly discovered Mut-driver genes that have been detected through genome-wide sequencing have often proved illuminating. For example, nearly half of these genes encode proteins that directly regulate chromatin through modification of histones or DNA. Examples include the histones HIST1H3B and H3F3A, as well as the proteins DNMT1 and TET1, which covalently modify DNA, EZH2, SETD2, and KDM6A, which, in turn, methylate or demethylate histones (53–57). These discoveries have profound implications for understanding the mechanistic basis of the epigenetic changes that are rampant in tumors (58). The discovery of genetic alterations in genes encoding mRNA splicing factors, such as *SF3B1* and *U2AF1* (59–61), was similarly stunning, as mutations in these genes would be expected to lead to a plethora of nonspecific cellular stresses rather than to promote specific tumor types. Another example is provided by mutations in the cooperating proteins ATRX and DAXX (62). Tumors with mutations in these genes all have a specific type of telomere elongation process termed “ALT” (for “alternative lengthening of telomeres”) (63). Though the ALT phenotype had been recognized for more than a decade, its genetic basis

was mysterious before the discovery of mutations of these genes and their perfect correlation with the ALT phenotype (64). A final example is provided by *IDH1* and *IDH2*, whose mutations have stimulated the burgeoning field of tumor metabolism (65) and have had fascinating implications for epigenetics (66, 67).

The Mut-driver genes listed in table S2A are affected by subtle mutations: base substitutions, intragenic insertions, or deletions. As noted above, Mut-driver genes can also be altered by less subtle changes, such as translocations, amplifications, and large-scale deletions. As with point mutations, it can be difficult to distinguish Mut-driver genes that are altered by these types of changes from genes that contain only passenger mutations. Genes that are not point-mutated, but are recurrently amplified (e.g., *MYC* family genes) or homozygously deleted (e.g., *MAP2K4*) and that meet other criteria (e.g., being the only gene in the amplicon or homozygously deleted region) are listed in table S2B. This adds 13 Mut-driver genes—10 oncogenes that are amplified and 3 tumor suppressor genes that are homozygously deleted—to the 125 driver genes that are affected by subtle mutations, for a total of 138 driver genes discovered to date (table S2).

Translocations provide similar challenges for driver classification. An important discovery related to this point is chromothripsis (68), a rare cataclysmic event involving one or a small number of chromosomes that results in a large number of chromosomal rearrangements. This complicates any inferences about causality, in the same way that mismatch repair deficiency compromises the interpretation of point mutations. However, for completeness, all fusion genes that have been identified in at least three independent tumors are listed in table S3. Virtually all of these genes were discovered through conventional approaches before the advent of genome-wide DNA sequencing studies, with some notable exceptions such as those described in (6) and (69). The great majority of these translocations are found in liquid tumors (leukemias and lymphomas) (table S3C) or mesenchymal tumors (table S3B) and were initially identified through karyotypic analyses. A relatively small number of recurrent fusions, the most important of which include *ERG* in prostate cancers (70) and *ALK* in lung cancers (71), have been described in more common tumors (table S3A).

Genes exist that predispose to cancer when inherited in mutant form in the germ line, but are not

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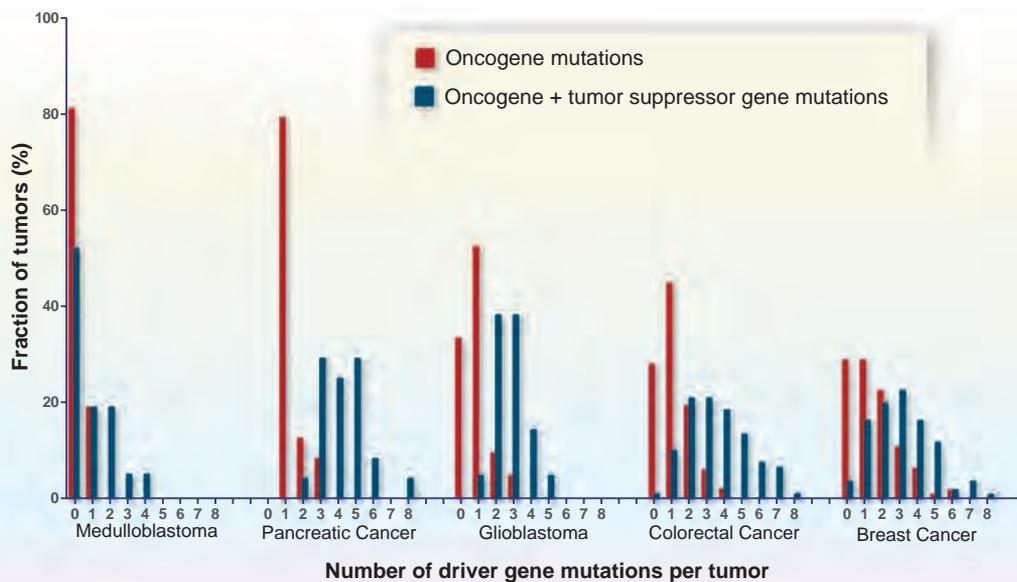


Fig. 5. Number and distribution of driver gene mutations in five tumor types. The total number of driver gene mutations [in oncogenes and tumor suppressor genes (TSGs)] is shown, as well as the number of oncogene mutations alone. The driver genes are listed in tables S2A and S2B. Translocations are not included in this figure, because few studies report translocations along with the other types of genetic alterations on a per-case basis. In the tumor types shown here, translocations affecting driver genes occur in less than 10% of samples. The published data on which this figure is based are provided in table S1E.

somatically mutated in cancer to a substantial degree. These genes generally do not confer an increase in selective growth advantage when they are abnormal, but they stimulate tumorigenesis in indirect ways (such as by increasing genetic instability, as discussed later in this Review). For completeness, these genes and the hereditary syndromes for which they are responsible are listed in table S4.

Dark Matter

Classic epidemiologic studies have suggested that solid tumors ordinarily require five to eight “hits,” now interpreted as alterations in driver genes, to develop (72). Is this number compatible with the molecular genetic data? In pediatric tumors such as medulloblastomas, the number of driver gene mutations is low (zero to two), as expected from the discussion above (Fig. 5). In common adult tumors—such as pancreatic, colorectal, breast, and brain cancers—the number of mutated driver genes is often three to six, but several tumors have only one or two driver gene mutations (Fig. 5). How can this be explained, given the widely accepted notion that tumor development and progression require multiple, sequential genetic alterations acquired over decades?

First, technical issues explain some of the “missing mutations.” Genome-wide sequencing is far from perfect, at least with the technologies available today. Some regions of the genome are not well represented because their sequences are difficult to amplify, capture, or unambiguously map to the genome (73–76). Second, there is usually a wide distribution in the number of times that a specific nucleotide in a given gene is observed in the sequence data, so some regions will not be well represented by chance factors alone (77). Finally, primary tumors contain not only neoplastic cells, but also stromal cells that dilute the signal from the mutated base, further reducing the probability of finding a mutation (78).

What fraction of mutations are missed by these three technical issues? A recent study of pancreatic cancers is informative in this regard. Biankin *et al.* used immunohistochemical and genetic analyses to select a set of primary tumor samples enriched in neoplastic cells (79). They used massively parallel sequencing to analyze the exomes of these samples, then compared their mutational data with a set of pancreatic cancer cell lines and xenografts in which mutations had previously been identified, using conventional Sanger sequencing, and confirmed to be present in the primary tumors (3, 16). Only 159 (63%) of the expected 251 driver gene mutations were identified in the primary tumors studied by next-generation sequencing alone, indicating a false-negative rate of 37%. Genome-wide studies in which the proportion of neoplastic cells within tu-

mors is not as carefully evaluated as in (79) will have higher false-negative rates. Moreover, these technical problems are exacerbated in whole-genome studies compared with exomic analyses, because the sequence coverage of the former is often lower than that of the latter (generally 30-fold in whole-genome studies versus more than 100-fold in exomic studies).

Conceptual issues also limit the number of detectable drivers. Virtually all studies, either at the whole-genome or whole-exome level, have focused on the coding regions. The reason for

interpret than the somatic mutations in cancers. The first examples of light coming to such dark matter have recently been published: Recurrent mutations in the promoter of the *TERT* gene, encoding the catalytic subunit of telomerase, have been identified and shown to activate its transcription (81, 82).

Mut-driver genes other than those listed in table S2 will undoubtedly be discovered as genome-wide sequencing continues. However, based on the trends noted above, most of the Mut-driver genes will likely be mountains in

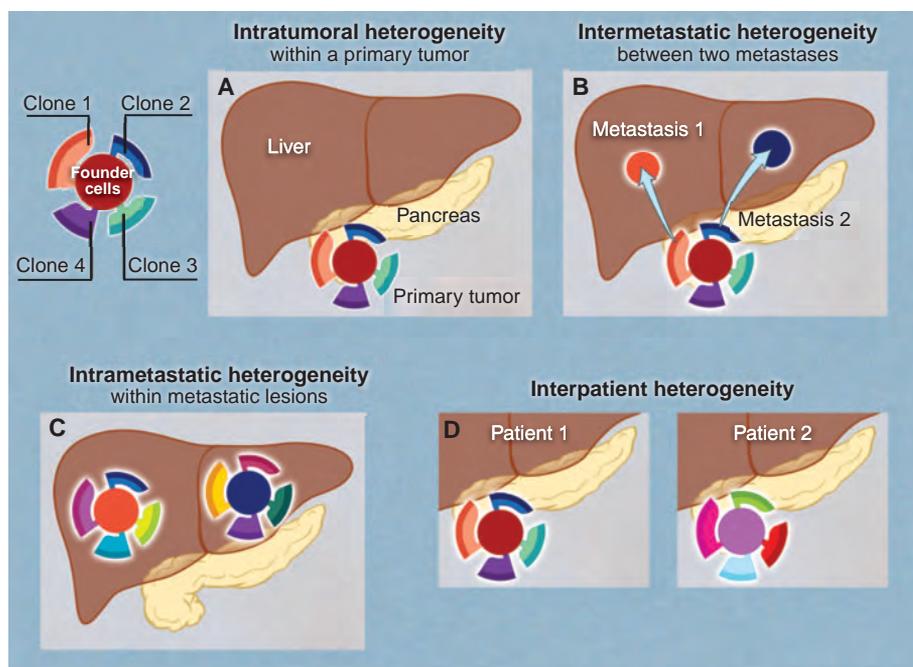


Fig. 6. Four types of genetic heterogeneity in tumors, illustrated by a primary tumor in the pancreas and its metastatic lesions in the liver. Mutations introduced during primary tumor cell growth result in clonal heterogeneity. At the top left, a typical tumor is represented by cells with a large fraction of the total mutations (founder cells) from which subclones are derived. The differently colored regions in the subclones represent stages of evolution within a subclone. (A) Intratumoral: heterogeneity among the cells of the primary tumor. (B) Intermetastatic: heterogeneity among different metastatic lesions in the same patient. In the case illustrated here, each metastasis was derived from a different subclone. (C) Intrametastatic: heterogeneity among the cells of each metastasis develops as the metastases grow. (D) Interpatient: heterogeneity among the tumors of different patients. The mutations in the founder cells of the tumors of these two patients are almost completely distinct (see text).

this is practical; it is difficult enough to identify driver gene mutations when they qualitatively alter the sequence of the encoded protein. Trying to make sense of intergenic or intronic mutations is much more difficult. Based on analogous studies of the identifiable mutations in patients with monogenic diseases, more than 80% of mutations should be detectable through analysis of the coding regions (80). However, this still leaves some mutations as unidentifiable “dark matter,” even in the germline genomes of heritable cases, which are usually easier to in-

terpret than the somatic mutations in cancers. rare tumor types or small hills in common tumor types; thus, these genes are unlikely to account for the bulk of the presumptive dark matter. Other types of dark matter can be envisioned, however. Copy-number alterations are ubiquitous in cancers, at either the whole-chromosome or subchromosomal levels. These alterations could subtly change the expression of their driver genes. Recent studies have suggested that the loss of one copy of chromosomes containing several tumor suppressor genes, each plausibly connected to neoplasia but not altered by

mutation, may confer a selective growth advantage (83, 84).

The most obvious source of dark matter is in Epi-driver genes. Human tumors contain large numbers of epigenetic changes affecting DNA or chromatin proteins. For example, a recent study of colorectal cancers showed that more than 10% of the protein-coding genes were differentially methylated when compared with normal colorectal epithelial cells (85). Some of these changes (i.e., those in Epi-driver genes) are likely to provide a selective growth advantage (86, 87). For example, epigenetic silencing of *CDK2NA* and *MLH1* is much more common than mutational inactivation of either of these two well-recognized driver genes (85). However, there is a critical difference between a genetic and an epigenetic change in a gene. Unlike the sequence of a gene in a given individual, methylation is plastic, varying with cell type, developmental stage, and patient age (21). The methylation state of the normal precursor cells that initiate tumorigenesis is unknown; these cells, such as normal stem cells, may represent only a tiny fraction of the cells in a normal organ. This plasticity also means that methylation can change under microenvironmental cues, such as those associated with low nutrient concentrations or abnormal cell contacts. It is therefore difficult to know whether specific epigenetic changes observed in cancer cells reflect, rather than contribute to, the neoplastic state. Criteria for distinguishing epigenetic changes that exert a selective growth advantage from those that do not (passenger epigenetic changes) have not yet been formulated. Given that Epi-driver genes are likely to compose a major component of the dark matter, further research on this topic is essential (58).

Genetic Heterogeneity

The mutations depicted in Fig. 1 are clonal; that is, they are present in the majority of the neoplastic cells in the tumors. But additional, subclonal (i.e., heterogeneous within the tumor) mutations are important for understanding tumor evolution. Four types of genetic heterogeneity are relevant to tumorigenesis (Fig. 6):

1) Intratumoral: heterogeneity among the cells of one tumor. This type of heterogeneity has been recognized for decades. For example, it is rare to see a cytogenetic study of a solid tumor in which all of the tumor cells display the same karyotype (88). The same phenomenon has been noted for individual genes [e.g., (89)] and more recently has been observed throughout the genome (16, 90–96). This kind of heterogeneity must exist: Every time a normal (or tumor) cell divides, it acquires a few mutations, and the number of mutations that distinguish any two cells simply marks the time from their last common ancestor (their founder cell). Cells at the opposite ends of large tumors will be spa-

tially distinct and, in general, will display more differences than neighboring cells (16). This phenomenon is analogous to speciation, wherein organisms on different islands are more likely to diverge from one another than are organisms on the same island.

In studies that have evaluated intratumoral heterogeneity by genome-wide sequencing, the majority of somatic mutations are present in all tumor cells. These mutations form the trunk of the somatic evolutionary tree. What is the importance of the mutations in the branches (i.e., those that are not shared by all tumor cells)? From a medical perspective, these mutations are often meaningless because the primary tumors are surgically removed. How much heterogeneity existed in the various branches before surgery is not important. However, this heterogeneity provides the seeds for intermetastatic heterogeneity, which is of great clinical importance.

2) Intermetastatic: heterogeneity among different metastatic lesions of the same patient. The vast majority of cancer patients die because their tumors were not removed before metastasis to surgically inaccessible sites, such as the liver, brain, lung, or bone. Patients who relapse with a single metastatic lesion can often still be cured by surgery or radiotherapy, but single metastases are the exception rather than the rule. A typical patient on a clinical trial has a dozen or more metastatic lesions large enough to be visualized by imaging, and many more that are smaller. If each of the metastatic lesions in a single patient was founded by a cell with a very different genetic constitution, then chemotherapeutic cures would be nearly impossible to achieve: Eradicating a subset of the metastatic lesions in a patient will not be adequate for long-term survival.

How much heterogeneity is there among different metastatic lesions? In short, a lot. It is not uncommon for one metastatic lesion to have 20 clonal genetic alterations not shared by other metastases in the same patient (16, 97). Because they are clonal, these mutations occurred in the founder cell of the metastasis; that is, the cell that escaped from the primary tumor and multiplied to form the metastasis. The founder cell for each metastasis is present in different, geographically distinct areas of the primary tumors, as expected (16).

This potentially disastrous situation is tempered by the fact that the heterogeneity appears largely confined to passenger gene mutations. In most of the studies documenting heterogeneity in malignancies, the Mut-driver genes are present in the trunks of the trees, though exceptions have been noted (95). These findings are consistent with the idea, discussed above, that the genetic alterations required for metastasis were present (i.e., selected for) before metastasis actually occurred. The data are also

consistent with the observation that in patients responsive to targeted agents, the response is often seen in all metastatic lesions rather than just a small subset (98).

3) Intrametastatic: heterogeneity among the cells of an individual metastasis. Each metastasis is established by a single cell (or small group of cells) with a set of founder mutations. As it grows, the metastasis acquires new mutations with each cell division. Though the founder mutations may make the lesion susceptible to antitumor agents, the new mutations provide the seeds for drug resistance. Unlike primary tumors, the metastatic lesions generally cannot be removed by surgery and must be treated with systemic therapies. Patients with complete responses to targeted therapies invariably relapse. Most of the initial lesions generally recur, and the time frame at which they recur is notably similar. This time course can be explained by the presence of resistance mutations that existed within each metastasis before the onset of the targeted therapy (99–102). Calculations show that any metastatic lesion of a size visible on medical imaging has thousands of cells (among the billions present) that are already resistant to virtually any drug that can be imagined (99, 101, 102). Thus, recurrence is simply a matter of time, entirely predictable on the basis of known mutation frequencies and tumor cell growth rates. This “fait accompli” can be circumvented, in principle, by treatment with multiple agents, as it is unlikely that a single tumor cell will be resistant to multiple drugs that act on different targets.

4) Interpatient: heterogeneity among the tumors of different patients. This type of heterogeneity has been observed by every oncologist; no two cancer patients have identical clinical courses, with or without therapy. Some of these differences could be related to host factors, such as germline variants that determine drug half-life or vascular permeability to drugs or cells, and some could be related to nongenetic factors (103). However, much of this interpatient heterogeneity is probably related to somatic mutations within tumors. Though several dozen somatic mutations may be present in the breast cancers from two patients, only a small number are in the same genes, and in the vast majority of cases, these are the Mut-driver genes (1, 104, 105). Even in these driver genes, the actual mutations are often different. Mutations altering different domains of a protein would certainly not be expected to have identical effects on cellular properties, as experimentally confirmed (106). Though it may seem that different mutations in adjacent codons would have identical effects, detailed studies of large numbers of patients have shown that this need not be the case. For example, a Gly¹²→Asp¹² (G12D) mutation of *KRAS* does not have the same clinical implications as a G13D mutation of the same gene (107). Interpatient heterogeneity has always been one of the major obstacles

to designing uniformly effective treatments for cancer. Efforts to individualize treatments based on knowledge of the genomes of cancer patients are largely based on an appreciation of this heterogeneity.

Signaling Pathways in Tumors

The immense complexity of cancer genomes that could be inferred from the data described above is somewhat misleading. After all, even advanced tumors are not completely out of control, as evidenced by the dramatic responses to agents that target mutant *BRAF* in melanomas (108) or mutant *ALK* in lung cancers (109). Albeit transient, these responses mean that interference with even a single mutant gene product is sufficient to stop cancer in its tracks, at least transiently. How can the genomic complexity of cancer be reconciled with these clinical observations?

Two concepts bear on this point. The first, mentioned above, is that >99.9% of the alterations in tumors (including point mutations, copy-number alterations, translocations, and epigenetic changes distributed throughout the genome, not just in the coding regions) are immaterial to neoplasia. They are simply passenger changes that mark the time that has elapsed between successive clonal expansions. Normal cells also undergo genetic alterations as they divide, both at the nucleotide and chromosomal levels. However, normal cells are programmed to undergo

cell death in response to such alterations, perhaps as a protective mechanism against cancer. In contrast, cancer cells have evolved to tolerate genome complexity by acquiring mutations in genes such as *TP53* (110). Thus, genomic complexity is, in part, the result of cancer, rather than the cause.

To appreciate the second concept, one must take the 30,000-foot view. A jungle might look chaotic at ground level, but the aerial view shows a clear order, with all the animals gathering at the streams at certain points in the day, and all the streams converging at a river. There is order in cancer, too. Mutations in all of the 138 driver genes listed in table S2 do one thing: cause a selective growth advantage, either directly or indirectly. Moreover, there appears to be only a limited number of cellular signaling pathways through which a growth advantage can be incurred (Fig. 7 and table S5).

All of the known driver genes can be classified into one or more of 12 pathways (Fig. 7). The discovery of the molecular components of these pathways is one of the greatest achievements of biomedical research, a tribute to investigators working in fields that encompass biochemistry, cell biology, and development, as well as cancer. These pathways can themselves be further organized into three core cellular processes:

1) Cell fate: Numerous studies have demonstrated the opposing relationship between cell division and differentiation, the arbiters of cell fate. Dividing cells that are responsible for populating normal tissues (stem cells) do not differentiate, and vice versa. Regenerative medicine is based on this distinction, predicated on ways to get differentiated cells to dedifferentiate into stem cells, then forcing the stem cells to differentiate into useful cell types for transplantation back into the patient. Many of the genetic alterations in cancer abrogate the precise balance between differentiation and division, favoring the latter. This causes a selective growth advantage, because differentiating cells eventually die or become quiescent. Pathways that function through this process include APC, HH, and NOTCH, all of which are well known to control cell fate in organisms ranging from worms to mammals (11). Genes encoding chromatin-modifying enzymes can also be included in this category. In normal development, the heritable switch from division to differentiation is not determined by mutation, as it is in cancer, but rather

by epigenetic alterations affecting DNA and chromatin proteins. What better way to subvert this normal mechanism for controlling tissue architecture than to debilitate the epigenetic modifying apparatus itself?

2) Cell survival: Though cancer cells divide abnormally because of cell-autonomous alterations, such as those controlling cell fate, their surrounding stromal cells are perfectly normal and do not keep pace. The most obvious ramification of this asymmetry is the abnormal vasculature of tumors. As opposed to the well-ordered network of arteries, veins, and lymphatics that control nutrient concentrations in normal tissues, the vascular system in cancers is tortuous and lacks uniformity of structure (112, 113). Normal cells are always within 100 μm of a capillary, but this is not true for cancer cells (114). As a result, a cancer cell acquiring a mutation that allows it to proliferate under limiting nutrient concentrations will have a selective growth advantage, thriving in environments in which its sister cells cannot. Mutations of this sort occur, for example, in the *EGFR*, *HER2*, *FGFR2*, *PDGFR*, *TGFBR2*, *MET*, *KIT*, *RAS*, *RAF*, *PIK3CA*, and *PTEN* genes (table S2A). Some of these genes encode receptors for the growth factors themselves, whereas others relay the signal from the growth factor to the interior of the cell, stimulating growth when activated (115, 116). For instance, mutations in *KRAS* or *BRAF* genes confer on cancer cells the ability to grow in glucose concentrations that are lower than those required for the growth of normal cells or of cancer cells that do not have mutations in these genes (117, 118). Progression through the cell cycle (and its antithesis, apoptosis) can be directly controlled by intracellular metabolites, and driver genes that directly regulate the cell cycle or apoptosis, such as *CDKN2A*, *MYC*, and *BCL2*, are often mutated in cancers. Another gene whose mutations enhance cell survival is *VHL*, the product of which stimulates angiogenesis through the secretion of vascular endothelial growth factor. What better way to provision growth factors to a rogue tumor than to lure the unsuspecting vasculature to its hideout?

3) Genome maintenance: As a result of the exotic microenvironments in which they reside, cancer cells are exposed to a variety of toxic substances, such as reactive oxygen species. Even without microenvironmental poisons, cells make mistakes while replicating their DNA or during division (119, 120), and checkpoints exist to either slow down such cells or make them commit suicide (apoptosis) under such circumstances (110, 121, 122). Although it is good for the organism to remove these damaged cells, tumor cells that can survive the damage will, by definition, have a selective growth advantage. Therefore, it is not surprising that genes whose mutations abrogate these checkpoints, such as *TP53* and *ATM*, are mutated in cancers

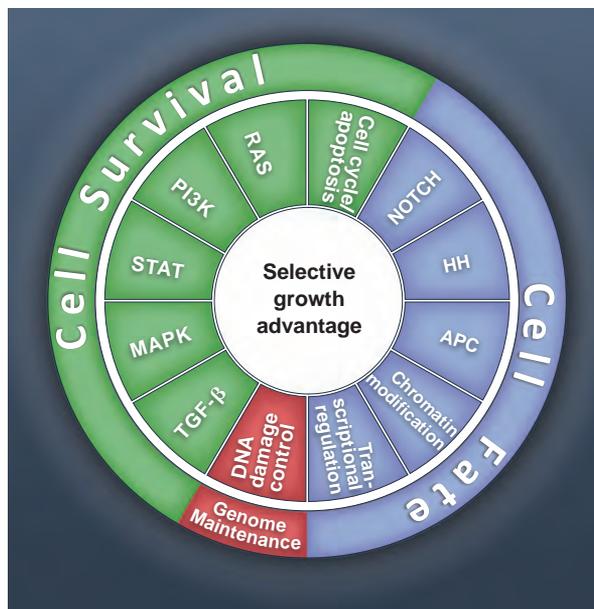


Fig. 7. Cancer cell signaling pathways and the cellular processes they regulate. All of the driver genes listed in table S2 can be classified into one or more of 12 pathways (middle ring) that confer a selective growth advantage (inner circle; see main text). These pathways can themselves be further organized into three core cellular processes (outer ring). The publications on which this figure is based are provided in table S5.

(123). Defects in these genes can also indirectly confer a selective growth advantage by allowing cells that have a gross chromosomal change favoring growth, such as a translocation or an extra chromosome, to survive and divide. Analogously, genes that control point mutation rates, such as *MLH1* or *MSH2*, are mutated in cancers (table S2A) or in the germ line of patients predisposed to cancers (table S4) because they accelerate the acquisition of mutations that function through processes that regulate cell fate or survival. What better way to promote cancer than by increasing the rate of occurrence of the mutations that drive the process?

Because the protein products of genes regulating cell fate, cell survival, and genome maintenance often interact with one another, the pathways within them overlap; they are not as discrete as might be inferred from the description above. However, grouping genes into pathways makes perfect sense from a genetics standpoint. Given that cancer is a genetic disease, the principles of genetics should apply to its pathogenesis. When performing a conventional mutagenesis screen in bacteria, yeast, fruit flies, or worms, one expects to discover mutations in several different genes that confer similar phenotypes. The products of these genes often interact with one another and define a biochemical or developmental pathway. Therefore, it should not be surprising that several different genes can result in the same selective growth advantage for cancer cells and that the products of these genes interact. The analogy between cancer pathways and biochemical or developmental pathways in other organisms goes even deeper: The vast majority of our knowledge of the function of driver genes has been derived from the study of the pathways through which their homologs work in nonhuman organisms. Though the functions are not identical to those in human cells, they are highly related and have provided the starting point for analogous studies in human cells.

Recognition of these pathways also has important ramifications for our ability to understand interpatient heterogeneity. One lung cancer might have an activating mutation in a receptor for a stimulatory growth factor, making it able to grow in low concentrations of epidermal growth factor (EGF). A second lung cancer might have an activating mutation in *KRAS*, whose protein product normally transmits the signal from the epidermal growth factor receptor (EGFR) to other cell signaling molecules. A third lung cancer might have an inactivating mutation in *NF1*, a regulatory protein that normally inactivates the *KRAS* protein. Finally, a fourth lung cancer might have a mutation in *BRAF*, which transmits the signal from *KRAS* to downstream kinases (Fig. 8). One would predict that mutations in the various components of a single pathway would be mutually exclusive—that is, not occurring in the

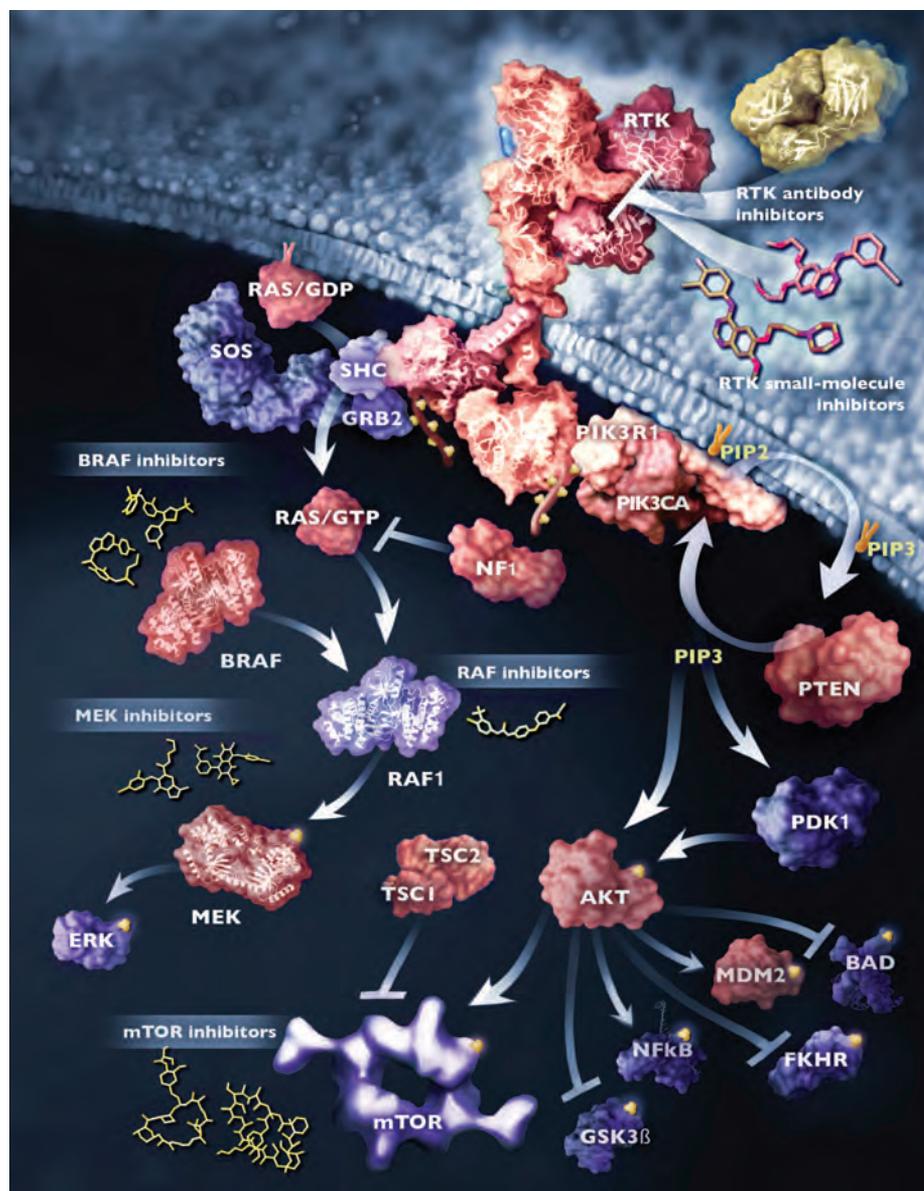


Fig. 8. Signal transduction pathways affected by mutations in human cancer. Two representative pathways from Fig. 7 (RAS and PI3K) are illustrated. The signal transducers are color coded: red indicates protein components encoded by the driver genes listed in table S2; yellow balls denote sites of phosphorylation. Examples of therapeutic agents that target some of the signal transducers are shown. RTK, receptor tyrosine kinase; GDP, guanosine diphosphate; MEK, MAPK kinase; ERK, extracellular signal-regulated kinase; NFkB, nuclear factor κ B; mTOR, mammalian target of rapamycin.

same tumor—and this has been experimentally confirmed (124, 125). Apart from being intellectually satisfying, knowledge of these pathways has implications for cancer therapy, as discussed in the next section.

A Perspective on Genome-Based Medicine in Oncology

Opportunities

Though cancer genome sequencing is a relatively new endeavor, it has already had an impact on the

clinical care of cancer patients. The recognition that certain tumors contain activating mutations in driver genes encoding protein kinases has led to the development of small-molecule inhibitor drugs targeting those kinases.

Representative examples of this type of genome-based medicine include the use of EGFR kinase inhibitors to treat cancers with *EGFR* gene mutations (126), the aforementioned anaplastic lymphoma kinase (ALK) inhibitors to treat cancers with *ALK* gene translocations (109), and specific inhibitors of mutant *BRAF* (109), and specific inhibitors of mutant *BRAF* (109), and specific inhibitors of mutant *BRAF* (109). Public Written Comments, Page 69

to treat cancers with *BRAF* mutations (108). Before instituting treatment with such agents, it is imperative to determine whether the cancer harbors the mutations that the drug targets. Only a small fraction of lung cancer patients have *EGFR* gene mutations or *ALK* gene translocations, and only these patients will respond to the drugs. Treating lung cancer patients without these particular genetic alterations would be detrimental, as such patients would develop the toxic side effects of the drugs while their tumors progressed.

A second type of genome-based medicine focuses on the side effects and metabolism of the therapeutic agents, rather than the genetic alterations they target. At present, the dose of cancer drugs given to patients is based on the patients' size (body weight or surface area). But the therapeutic ratio of cancer drugs (ratio of the concentration that causes side effects to the concentration required to kill tumor cells) is generally low, particularly for conventional (nontargeted) therapeutic agents. Small changes in circulating concentrations of these drugs can make the difference between substantial tumor regression and intolerable side effects. Interrogation of the germline status of the genes encoding drug-metabolizing enzymes could substantially improve the outcomes of treatment by informing drug dosing (127). Optimally, this genome interrogation would be accompanied by pharmacokinetic measurements of drug concentrations in each patient. The additional cost of such analyses would be small compared with the exorbitant costs of new cancer therapies—for recently approved drugs, the cost is estimated to be \$200,000 to \$300,000 per quality life year produced (128).

Challenges

One challenge of genome-based medicine in oncology is already apparent from the opportunities described above: All of the clinically approved drugs that target the products of genetically altered genes are directed against kinases. One reason for this is that kinases are relatively easy to target with small molecules and have been extensively studied at the biochemical, structural, and physiologic levels (129). But another reason has far deeper ramifications. The vast majority of drugs on the market today, for cancer or other diseases, inhibit the actions of their protein targets. This inhibition occurs because the drugs interfere with the protein's enzymatic activity (such as the phosphorylation catalyzed by kinases) or with the binding of the protein to a small ligand (such as with G protein-coupled receptors). Only 31 of the oncogenes listed in tables S2 and S3 have enzymatic activities that are targetable in this manner. Many others participate in protein complexes, involving large interfaces and numerous weak interactions. Inhibiting the function of such proteins

with small drugs is notoriously difficult because small compounds can only inhibit one of these interactions (130, 131).

Though one can at least imagine the development of drugs that inhibit nonenzymatic protein functions, the second challenge evident from table S2 poses even greater difficulties: A large fraction of the Mut-driver genes encode tumor suppressors. Drugs generally interfere with protein function; they cannot, in general, replace the function of defective genes such as those resulting from mutations in tumor suppressor genes. Unfortunately, tumor suppressor gene-inactivating mutations predominate over oncogene-activating mutations in the most common solid tumors: Few individual tumors contain more than one oncogene mutation (Fig. 5).

The relatively small number of oncogene mutations in tumors is important in light of the intrametastatic heterogeneity described earlier. To circumvent the inevitable development of resistance to targeted therapies, it will likely be necessary to treat patients with two or more drugs. The probability that a single cancer cell within a large metastatic lesion will be resistant to two agents that target two independent pathways is exponentially less than the probability that the cell will be resistant to a single agent. However, if the cancer cell does not contain more than one targetable genetic alteration (i.e., an oncogene mutation), then this combination strategy is not feasible.

Given the paucity of oncogene alterations in common solid tumors and these principles, can

targeted therapeutic approaches ever be expected to induce long-term remissions, even cures, rather than the short-term remissions now being achieved? The saviors are pathways; every tumor suppressor gene inactivation is expected to result in the activation of some growth-promoting signal downstream of the pathway. An example is provided by *PTEN* mutations: Inactivation of the tumor suppressor gene *PTEN* results in activation of the AKT kinase (Fig. 8). Similarly, inactivation of the tumor suppressor gene *CDKN2A* results in activation of kinases, such as cyclin-dependent kinase 4, that promote cell cycle traverse (132). Furthermore, inactivation of tumor suppressor gene *APC* results in constitutive activity of oncogenes such as *CTNNB1* and *CMYC* (133–135).

We believe that greater knowledge of these pathways and the ways in which they function is the most pressing need in basic cancer research. Successful research on this topic should allow the development of agents that target, albeit indirectly, defective tumor suppressor genes. Indeed, there are already examples of such indirect targeting. Inactivating mutations of the tumor suppressor genes *BRCA1* or *BRCA2* lead to activation of downstream pathways required to repair DNA damage in the absence of BRCA function. Thus, cancer cells with defects in *BRCA1* or *BRCA2* are more susceptible to DNA damaging agents or to drugs that inhibit enzymes that facilitate the repair of DNA damage such as PARP [poly(adenosine diphosphate-ribose) polymerase] (136). PARP inhibitors have shown

Box 2. Highlights

1. Most human cancers are caused by two to eight sequential alterations that develop over the course of 20 to 30 years.
2. Each of these alterations directly or indirectly increases the ratio of cell birth to cell death; that is, each alteration causes a selective growth advantage to the cell in which it resides.
3. The evidence to date suggests that there are ~140 genes whose intragenic mutations contribute to cancer (so-called Mut-driver genes). There are probably other genes (Epi-driver genes) that are altered by epigenetic mechanisms and cause a selective growth advantage, but the definitive identification of these genes has been challenging.
4. The known driver genes function through a dozen signaling pathways that regulate three core cellular processes: cell fate determination, cell survival, and genome maintenance.
5. Every individual tumor, even of the same histopathologic subtype as another tumor, is distinct with respect to its genetic alterations, but the pathways affected in different tumors are similar.
6. Genetic heterogeneity among the cells of an individual tumor always exists and can impact the response to therapeutics.
7. In the future, the most appropriate management plan for a patient with cancer will be informed by an assessment of the components of the patient's germline genome and the genome of his or her tumor.
8. The information from cancer genome studies can also be exploited to improve methods for prevention and early detection of cancer, which will be essential to reduce cancer morbidity and mortality.

encouraging results in clinical trials when used in patients whose tumors have inactivating mutations of BRCA genes (137).

Further progress in this area will require more detailed information about the signaling pathways through which cancer genes function in human cancer cells, as well as in model organisms. One of the lessons of molecular biology over the past two decades is that pathway functions are different, depending on the organism, cell type, and precise genetic alterations in that cell (138). A pertinent example of this principle is provided by results of treatment with drugs inhibiting mutant BRAF kinase activity. In the majority of patients with melanomas harboring (V600E; V, Val; E, Glu) mutations in the BRAF gene, these drugs induce dramatic (though transient) remissions (108). But the same drugs have no therapeutic effect in colorectal cancer patients harboring the identical BRAF mutations (139). This observation has been attributed to the expression of EGFR, which occurs in some colorectal cancers but not in melanoma and is thought to circumvent the growth-inhibitory effects of the BRAF inhibitors. With this example in mind, no one should be surprised that a new drug that works well in an engineered tumor in mice fails in human trials; the organism is different, the cell type is usually different, and the precise genetic constitutions are always different. The converse of this statement—that a drug that fails in animal trials will not necessarily fail in human trials—has important practical consequences. In our view, if the biochemical and conceptual bases for a drug's actions are solid and the drug is shown to be safe in animals, then a human trial may be warranted, even if it does not shrink tumors in mice.

Genome-Based Medicines of the Future

Cancer genomes can also be exploited for the development of more effective immunotherapies. As noted above, typical solid tumors contain 30 to 70 mutations that alter the amino acid sequences of the proteins encoded by the affected genes. Each of these alterations is foreign to the immune system, as none have been encountered during embryonic or postnatal life. Therefore, these alterations, in principle, provide a “holy grail” for tumor immunology: truly tumor-specific antigens. These antigens could be incorporated into any of the numerous platforms that already exist for the immunotherapy of cancer. These include administration of vaccines containing the mutant peptide, viruses encoding the mutant peptides on their surfaces, dendritic cells presenting the mutated peptide, and antibodies or T cells with reactivity directed against the mutant peptides (140).

To realize these sorts of therapeutics, several conditions must be met. First, the mutant protein must be expressed. As cancer cells generally express about half of the proteins that are encoded

by the human genome (141), this condition is not limiting. Second, as most proteins affected by mutations are intracellular, these mutations will not be visible to the immune system unless the mutant residue is presented in the context of a human leukocyte antigen (HLA) protein. Based on in silico analyses of binding affinities, it has been estimated that a typical breast or colorectal cancer contains 7 to 10 mutant proteins that can bind to an individual patient's HLA type (142). These theoretical predictions have recently gained experimental support. Studies of mouse tumors have identified mutant genes and shown that the corresponding peptides can induce antitumor immunity when administered as vaccines (143). Moreover, clinical trials of brain cancer patients immunized against a mutant peptide have yielded encouraging results (144).

As with all cancer therapies that are attractive in concept, obstacles abound in practice. If a tumor expresses a mutant protein that is recognizable as foreign, why has the host immune system not eradicated that tumor already? Indeed, immunoediting in cancers has been shown to exist, resulting in the down-regulation or absence of mutant epitopes that should have, and perhaps did, elicit an immune response during tumor development (145, 146). Additionally, tumors can lose immunogenicity through a variety of genetic alterations, thereby precluding the presentation of epitopes that would otherwise be recognized as foreign (147). Though these theoretical limitations are disheartening, recent studies on immune regulation in humans portend cautious optimism (148, 149).

Other Ways to Reduce Morbidity and Mortality Through Knowledge of Cancer Genomics

When we think about eradicating cancer, we generally think about curing advanced cases—those that cannot be cured by surgery alone because they have already metastasized. This is a curious way of thinking about this disease. When we think of cardiovascular or infectious diseases, we first consider ways to prevent them rather than drugs to cure their most advanced forms. Today, we are in no better position to cure polio or massive myocardial infarctions than we were a thousand years ago. But we can prevent these diseases entirely (vaccines), reduce incidence (dietary changes, statins), or mitigate severity (stents, thrombolytic agents) and thereby make a major impact on morbidity and mortality.

This focus on curing advanced cancers might have been reasonable 50 years ago, when the molecular pathogenesis of cancers was mysterious and when chemotherapeutic agents against advanced cancers were showing promise. But this mindset is no longer acceptable. We now know precisely what causes cancer: a sequential series of alterations in well-defined genes that

alter the function of a limited number of pathways. Moreover, we know that this process takes decades to develop and that the incurable stage, metastasis, occurs only a few years before death. In other words, of the one million people that will die from cancer this year, the vast majority will die only because their cancers were not detected in the first 90% of the cancers' lifetimes, when they were amenable to the surgeons' scalpel.

This new knowledge of cancer (Box 2) has reinvigorated the search for cures for advanced cancers, but has not yet permeated other fields of applied cancer research. A common and limited set of driver genes and pathways is responsible for most common forms of cancer (table S2); these genes and pathways offer distinct potential for early diagnosis. The genes themselves, the proteins encoded by these genes, and the end products of their pathways are, in principle, detectable in many ways, including analyses of relevant body fluids, such as urine for genitourinary cancers, sputum for lung cancers, and stool for gastrointestinal cancers (150). Equally exciting are the possibilities afforded by molecular imaging, which not only indicate the presence of a cancer but also reveal its precise location and extent. Additionally, research into the relationship between particular environmental influences (diet and lifestyle) and the genetic alterations in cancer is sparse, despite its potential for preventative measures.

The reasons that society invests so much more in research on cures for advanced cancers than on prevention or early detection are complex. Economic issues play a part: New drugs are far more lucrative for industry than new tests, and large individual costs for treating patients with advanced disease have become acceptable, even in developing countries (151). From a technical standpoint, the development of new and improved methods for early detection and prevention will not be easy, but there is no reason to assume that it will be more difficult than the development of new therapies aimed at treating widely metastatic disease.

Our point is not that strenuous efforts to develop new therapies for advanced cancer patients should be abandoned. These will always be required, no matter our arsenal of early detection or preventative measures. Instead, we are suggesting that “plan A” should be prevention and early detection, and “plan B” (therapy for advanced cancers) should be necessary only when plan A fails. To make plan A viable, government and philanthropic organizations must dedicate a much greater fraction of their resources to this cause, with long-term considerations in mind. We believe that cancer deaths can be reduced by more than 75% in the coming decades (152), but that this reduction will only come about if greater efforts are made toward early detection and prevention.

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Supplementary Materials

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Regulation of intergovernmental relations

From: "Dr. Vladimir Grinev" [REDACTED]

Date: Thu, November 14, 2013 1:47 pm

To: pcast@ostp.gov

President's Council of Advisors on Science and Technology (PCAST)

Ladies and Gentleman,

Foundation for the development of Russia offer the Council the Megaproject of communicative integration of Europe and Asia.

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Please contact my representative in Berlin (Germany) Dr. Vladimir Grinev in case of your interest.

Kind regards,

E.M. Grinev

President of the Foundation for the development of Russia

Doctor of Engineering, Doctor of Economics

Dr.-Eng. Vladimir Grinev Tel. [REDACTED]