

Volume 3 | Issue 1 Manuscript 1114

2017

The Journey to Competency-based Medical Education - Implementing **Milestones**

Eric S. Holmboe

Follow this and additional works at: https://mds.marshall.edu/mjm



Part of the Medical Education Commons

Recommended Citation

Holmboe, Eric S. (2017) "The Journey to Competency-based Medical Education - Implementing Milestones," Marshall Journal of Medicine: Vol. 3: Iss. 1, Article 2.

DOI: http://dx.doi.org/10.18590/mjm.2017.vol3.iss1.2

Available at: https://mds.marshall.edu/mjm/vol3/iss1/2

DOI: http://dx.doi.org/10.18590/mjm.2017.vol3.iss1.2

Open Access | © 0

 $This \ commentary \ is \ available \ in \ Marshall \ Journal \ of \ Medicine: \ https://mds.marshall.edu/mjm/vol3/iss1/2$

References with DOI

- 1. Batalden P, Leach D, Swing S, Dreyfus H, Dreyfus S. General competencies and accreditation in graduate medical education. Health Aff. 2002; 21: 103-111. https://doi.org/10.1377/hlthaff.21.5.103
- 2. Carraccio C, Wolfsthal SD, Englander R, Ferentz K, Martin C. Shifting paradigms: from Flexner to competencies. Acad Med. 2002 May;77(5):361-7. https://doi.org/10.1097/00001888-200205000-00003
- 3. Pusic MV, Boutis K, Hatala R, Cook DA. Learning curves in health professions education. Acad Med. 2015 Aug;90(8):1034-42 https://doi.org/10.1097/acm.000000000000081
- 4. Green ML, Aagaard EM, Caverzagie KJ, Chick DA, Holmboe ES, Kane G, Smith CD, lobst W. Charting the Road to Competence: Developmental Milestones for Internal Medicine Residency Training. J Graduate Med Educ. 2009; 1: 5-20. https://doi.org/10.4300/01.01.0003
- 5. Philibert I, Brigham T, Edgar L, Swing S. Organization of the educational milestones for use in the assessment of educational outcomes. J Grad Med Educ. 2014 Mar;6(1):177-82. https://doi.org/10.4300/jgme-06-01-35
- 6. Nabors C, Peterson SJ, Aronow W, Sute S, Mumtaz A, Delorenzo L, Chandy D, Lehman S, Frishman WH, Holmboe ES. Operationalizing the Internal Medicine Milestones An Early Status Report. J Grad Medical Educ. 2013; 5: 130-137. https://doi.org/10.4300/jgme-d-12-00130.1
- 7. Li ST, Tancredi DJ, Schwartz A, Guillot AP, Burke AE, Trimm RF, Guralnick S, Mahan JD, Gifford KA; Association of Pediatric Program Directors (APPD) Longitudinal Educational Assessment Research Network (LEARN) Validity of Resident Self-Assessment Group. Competent for Unsupervised Practice: Use of Pediatric Residency Training Milestones to Assess Readiness. Acad Med. 2016 Jul 26. [Epub ahead of print]. https://doi.org/10.1097/acm.000000000000001322
- 8. Beeson M, Holmboe E, Korte R, Nasca T, Brigham T, Russ C, Whitley C, Reisdorff E. Initial Validity Analysis of the Emergency Medicine Milestones. Acad Emerg Med. 2015 Jul;22(7):838-44. https://doi.org/10.1111/acem.12697
- 9. Hauer KE, Clauser J, Lipner RS, Holmboe ES, Caverzagie K, Hamstra SJ, Hood S, Iobst W, Warm E, McDonald FS. The Internal Medicine Reporting Milestones: Cross-sectional Description of Initial Implementation in U.S. Residency Programs. Ann Intern Med. 2016;165(5):356-62. https://doi.org/10.7326/m15-2411
- 10. Hauer KE, Vandergrift J, Hess B, Lipner RS, Holmboe ES, Hood S, Iobst W, Hamstra SJ, McDonald FS.Correlations Between Ratings on the Resident Annual Evaluation Summary and the Internal Medicine Milestones and Association With ABIM Certification Examination Scores Among US Internal Medicine Residents, 2013-2014. JAMA. 2016;316(21):2253-2262. https://doi.org/10.1001/jama.2016.17357
- 11. Witteles RM, Verghese A. Accreditation Council for Graduate Medical Education (ACGME) Milestones-Time for a Revolt? JAMA Intern Med. 2016;176(11):1599-1600. https://doi.org/10.1001/jamainternmed.2016.5552
- 12. Norman G, Norcini J, Bordage G. Competency-based education: milestones or millstones? J Grad Med

Educ. 2014 Mar;6(1):1-6 https://doi.org/10.4300/jgme-d-13-00445.1

- 13. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008 29;337(sep29 1):a1655–a1655. https://doi.org/10.1136/bmj.a1655
- 14. Holmboe ES, Call S, Ficalora RD. Milestones and Competency-Based Medical Education in Internal Medicine. JAMA Intern Med. 2016;176(11):1601-1602 https://doi.org/10.1001/jamainternmed.2016.5556
- 15. Pawson R, Greenhalgh T, Harvey G, Walshe K. 2005. Realist review A new method of systematic review designed for complex policy interventions. J Health Serv Res Policy 10(Suppl. 1):21–34. https://doi.org/10.1258/1355819054308530
- 16. Ericsson KA. Deliberate practice and the acquisition and maintenance of expert performance in medicine and related domains. Acad Med. 2004;79(10 Suppl):S70-81. https://doi.org/10.1097/00001888-200410001-00022
- 17. Nelson EC, Batalden PB, Godfrey MM. Quality by Design. A Clinical Microsystems Approach. Jossey-Bass. San Francisco. 2007.
- 18. Nasca TJ, Philibert I, Brigham T, Flynn TC. The next GME accreditation system-rationale and benefits. N Engl J Med. 2012 Mar 15;366(11):1051-6. https://doi.org/10.1056/nejmsr1200117

Commentary: The journey to competency-based medical education - implementing milestones

Eric S. Holmboe, MD¹

Author Affiliations:

1. Accreditation Council for Graduate Medical Education

Disclosures: Eric Holmboe works for the Accreditation Council for Graduate Medical Education and receives royalties for a textbook from Mosby-Elsevier.

Corresponding Author:

Eric S. Holmboe. MD Accreditation Council for Graduate Medical Education Chicago, IL

Email: eholmboe@acgme.org

Commentary

Competency-based medical education has taken root in many countries. In the United States, the six general competencies (Box 1) were formally approved by the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Medical Specialties (ABMS) in February 1999 (P. Batalden, personal communication). The competencies served as the foundation of the Outcomes Project launched by the ACGME in 2001¹. Residency and fellowship programs were expected to use the competency framework to innovate and improve curricula and assessments, especially in areas that had not previously received adequate attention in training such as quality improvement, patient safety, and interprofessional teamwork to name a few.

Box 1 - The Six General Competencies

Patient care and procedural skills Medical knowledge Interpersonal skills and communication Professionalism Practice-based learning and improvement Systems-based practice

Implementation of the new competency framework was difficult and programs struggled to revise or develop new curricula and assessments. For example, faculty struggled with assessments of professionalism and teamwork and to understand the newer competencies of practice-based learning and improvement and systems-based practice. Many of the terms and concepts of these two new competencies were unfamiliar to faculty because few had prior experience in these competency domains during their own residency and fellowship training. In short, most specialty disciplines lacked a shared mental model of the competencies. Furthermore, most programs were structured around a time and breadth-based curriculum that struggled to incorporate the concepts of longitudinal professional development and learning curves.^{2,3}

To help address some of these challenges, the ACGME embarked on the development of Milestones in 2010 after a successful pilot project conducted in Internal Medicine between 2007 to 2009.⁴ The Milestones are intentionally designed to help create a developmental language (i.e. a shared mental model) for the six general competencies within a discipline. All the specialty disciplines created their own Milestone sets between 2010 and 2013, and in July 2013 seven specialties began implementation of their Milestones.⁵ While some early successes and validity evidence have been published, implementation of the Milestones remains a challenge for many programs.⁶⁻¹²

One major reason for these struggles is the complexity involved in implementing Milestones. In essence, Milestones represent a complex intervention. The Medical Research Council in the United Kingdom defined a complex intervention as simply, "interventions with several interacting components." Milestones are designed to serve multiple purposes. For the residency program, Milestones are an important framework, or rubric, to guide curricular change, development of better assessment methods and tools, and the identification of trainees-in-

difficulty more effectively and earlier while serving as the guideline for conversation at the clinical competency committee. For residents, Milestones are intended to lead to more self-directed assessment, better and more systematic feedback, and to help guide their own individual learning plans and development. Thus, it is not hard to see how the multiple purposes of the Milestone components will affect multiple other components of a training program.

Medical education is a complex enterprise with multiple interacting parts. Furthermore, interventions in post-graduate medical education occur in the context of complex social systems that most importantly provide care to patients and families as part of the experiential educational process. Milestones therefore must function in the service of both learners and patients. Viewing Milestones as a service intervention can help us to understand both the implementation barriers and facilitators in these still early days of moving to a competency-based educational model.

To dive deeper into how Milestones might function as a complex service intervention, I will turn to a framework Pawson and colleagues used in the context of evaluating health care and policy interventions. First, Milestones, like any complex intervention, operate on the hypothesis that if they are implemented (successfully) they will facilitate improved educational outcomes of learners and ultimately improve patient care outcomes. Milestones are importantly grounded in several educational theories of professional development. Early validity research studies are encouraging in supporting the use of Milestones professional development. As a sufficient number of residents graduate and enter practice we will be able to examine the links, or associations, between Milestone performance and quality of practice: the ultimate outcome goal of the Milestone initiative.

Second, complex service interventions by definition are active, "that is, they achieve their effects via the active input of [multiple] individuals (clinicians, educators, managers, patients [and learners])." ¹⁵All these individuals possess volition and we must recognize that the knowledge, skills and actions of all these interdependent actors will affect how Milestones are used and whether Milestones achieve their intended purposes within a program. Implementation of any change requires a coalition with shared goals. Too often in medical education we do not take sufficient time to reflect and try to understand the various roles and actions of individuals when implementing a change and building change coalitions.

Third, complex service interventions have a "long journey;" Milestones are no different. ¹⁵ The current set of Milestones are truly version 1.0 and future revisions will be essential as learning about what works, for whom, in what circumstances, and why accrues. Milestones started as a community driven project to define the sub-competencies and developmental language over nine years ago. ⁴ Over the past 4 years Milestones have transitioned for use by each residency program and have involved a series of new or revised activities such as clinical competency committees. ¹⁴ As Pawson and colleagues note, "the success of an intervention thus depends on the cumulative success of the entire sequence of mechanisms as the [intervention] unfolds." ¹⁵ Thus, Milestones must be an iterative journey involving collaboration and co-production between producers, accreditors, and those implementing Milestones on the front lines.

Fourth, implementation chains for complex service interventions are non-linear. Non-linearity is a hallmark of all complex systems. Non-linearity can mean "large" interventions may have little

to modest impact while, conversely, small interventions have large impact. Complex interventions in the early phases of systems can actually cause regression (i.e. things get worse) as the actors in the system grapple with the changes necessary for effective implementation. The individuals within the system can also differentially affect the implementation, from institutional leadership to the learners. It is important to monitor the relative influence and actions of all individuals involved in the implementation process in order to make iterative adjustments.

Fifth, complex service interventions such as Milestones are very fragile as they are embedded in multiple, dynamic social systems. In medicine, many of these social systems are organized as microsystems. As defined by Nelson and colleagues, a microsystem is simply a "combination of a small group of people who work together on a regular basis to provide care and the subpopulation of patients who receive that care. It has clinical and business aims, linked processes, and a shared information environment, and it produces services and care that can be measured as performance outcomes." Many training microsystems are geographically located within hospitals, such as the emergency department, hospital ward, radiology suite, operating theatre and so on. Our residents encounter multiple microsystems every day. These microsystems have profound influence on residents' experiential learning and assessment along with the social milieu of the clinical competency committee, the residency program, etc.

Sixth, complex service interventions will typically "mutate" based on local context and needs and not be implemented as entirely intended. Some refer to this as fidelity of implementation, but each program will confront its own contextual realities and make changes. Thus, we can fully expect that Milestones will be implemented in a "mutating fashion shaped by refinement, reinvention, and adaption to local circumstances." In is not necessarily a "bad thing," but rather represents the reality of using a framework such as Milestones in literally thousands of contexts. This observation calls out the need to embrace the likelihood of mutation as a learning opportunity that can guide the ongoing study and refinement of Milestones at the local and national level.

Finally, complex service interventions operate and function as "open systems that will feed back on themselves." The activities of implementation will themselves lead to further changes as learning occurs among those both performing and being affected by the intervention. This learning and ongoing change is part of the long journey, as well as the mutability and fragility of complex interventions such as Milestones. Table 1 summarizes the seven characteristics of complex interventions and the implications for Milestones implementation.

Table 1: Characteristics and Implications of Complex Service Interventions (CSIs)

CSIs operate on the hypothesis that if they are implemented effectively they will produce positive change CSIs are active CSIs are active CSIs have a long journey Transforming graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Competencies and Milestones are grounded in sound educational theory, but will require application of implementation will require application of implementation of implementation of application and colong in graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
implemented effectively they will produce positive change sound educational theory, but will require application of implementation theories to be most effective. CSIs are active Implementation requires the interdependent actions of multiple individuals. Implementation of any change requires a coalition with shared goals. CSIs have a long journey Transforming graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
positive change application of implementation theories to be most effective. CSIs are active Implementation requires the interdependent actions of multiple individuals. Implementation of any change requires a coalition with shared goals. CSIs have a long journey Transforming graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
CSIs are active Implementation requires the interdependent actions of multiple individuals. Implementation of any change requires a coalition with shared goals. CSIs have a long journey Transforming graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
CSIs are active Implementation requires the interdependent actions of multiple individuals. Implementation of any change requires a coalition with shared goals. CSIs have a long journey Transforming graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
actions of multiple individuals. Implementation of any change requires a coalition with shared goals. CSIs have a long journey Transforming graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
CSIs have a long journey Transforming graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
CSIs have a long journey Transforming graduate medical education is a long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
long, iterative process involving multiple stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
stakeholders. This long journey requires a commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
commitment on the part of all stakeholders to embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
embrace change and engage in collaboration and co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
co-production through civil discourse. Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
Implementation chains for complex service interventions are also non-linear Implementation of competencies and Milestones will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
interventions are also non-linear will not be a simple, stepwise process. There will be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
be "ups and downs" along the journey. Some implementation strategies will be more impactful than others and not always related to the
implementation strategies will be more impactful than others and not always related to the
than others and not always related to the
•
1, 1 0 00 . 1 1 1 T. 1444 1 4
magnitude of effort involved. It will be essential
moving forward for the entire community to learn
what triggers small and large intended and
unintended effects.
CSIs are very fragile Any change process, such as implementing
Milestones, is fragile and can be easily disrupted
by institutional changes, unanticipated events,
frustration, inability to let go of ineffective
approaches and cynicism. As a collective
educational community we must work together to
work through and avoid such pitfalls.
CSIs are prone to mutate Milestones will change and "mutate" over time as
they must. The current set of Milestones has
always been labeled "version 1.0." There was a
full realization they will need to change as
programs learn, mutate and change Milestones
during these early phases of implementation.
CSIs operate and function as "open systems that There are multiple important feedback loops
will feed back on themselves." involving Milestones: feedback to and with
residents and fellows; feedback within programs
to help programs continually improve; feedback
to help whole specialties evolve and improve
through national reporting of Milestones data.

What does all this mean moving forward? First and foremost, we must see Milestones as but one component of a larger, complex initiative to facilitate transformation in graduate medical education. We are now 17 years into the competency movement in the United States, having reached a new inflection point in the "long journey" with the introduction of Milestones. Attending to the seven characteristics of complex service interventions while implementing and

evolving Milestones as a useful component of medical education can serve to enhance their potential effectiveness. Much remains to be done, but the ultimate effectiveness of Milestones, along with other relevant changes in residency and fellowship programs, will depend on a collaborative, co-production process with all stakeholders, including the ACGME.¹⁸

References

- 1. Batalden P, Leach D, Swing S, Dreyfus H, Dreyfus S. General competencies and accreditation in graduate medical education. Health Aff. 2002; 21: 103-111.
- 2. Carraccio C, Wolfsthal SD, Englander R, Ferentz K, Martin C. Shifting paradigms: from Flexner to competencies. Acad Med. 2002 May;77(5):361-7.
- 3. Pusic MV, Boutis K, Hatala R, Cook DA. Learning curves in health professions education. Acad Med. 2015 Aug;90(8):1034-42
- 4. Green ML, Aagaard EM, Caverzagie KJ, Chick DA, Holmboe ES, Kane G, Smith CD, Iobst W. Charting the Road to Competence: Developmental Milestones for Internal Medicine Residency Training. J Graduate Med Educ. 2009; 1: 5-20.
- 5. Philibert I, Brigham T, Edgar L, Swing S. Organization of the educational milestones for use in the assessment of educational outcomes. J Grad Med Educ. 2014 Mar;6(1):177-82.
- 6. Nabors C, Peterson SJ, Aronow W, Sute S, Mumtaz A, Delorenzo L, Chandy D, Lehman S, Frishman WH, Holmboe ES. Operationalizing the Internal Medicine Milestones An Early Status Report. J Grad Medical Educ. 2013; 5: 130-137.
- 7. Li ST, Tancredi DJ, Schwartz A, Guillot AP, Burke AE, Trimm RF, Guralnick S, Mahan JD, Gifford KA; Association of Pediatric Program Directors (APPD) Longitudinal Educational Assessment Research Network (LEARN) Validity of Resident Self-Assessment Group. Competent for Unsupervised Practice: Use of Pediatric Residency Training Milestones to Assess Readiness. Acad Med. 2016 Jul 26. [Epub ahead of print].
- 8. Beeson M, Holmboe E, Korte R, Nasca T, Brigham T, Russ C, Whitley C, Reisdorff E. Initial Validity Analysis of the Emergency Medicine Milestones. Acad Emerg Med. 2015 Jul;22(7):838-44.
- 9. Hauer KE, Clauser J, Lipner RS, Holmboe ES, Caverzagie K, Hamstra SJ, Hood S, Iobst W, Warm E, McDonald FS. The Internal Medicine Reporting Milestones: Cross-sectional Description of Initial Implementation in U.S. Residency Programs. Ann Intern Med. 2016;165(5):356-62.
- 10. Hauer KE, Vandergrift J, Hess B, Lipner RS, Holmboe ES, Hood S, Iobst W, Hamstra SJ, McDonald FS. Correlations Between Ratings on the Resident Annual Evaluation Summary and the Internal Medicine Milestones and Association With ABIM Certification Examination Scores Among US Internal Medicine Residents, 2013-2014. JAMA. 2016;316(21):2253-2262.
- 11. Witteles RM, Verghese A. Accreditation Council for Graduate Medical Education (ACGME) Milestones-Time for a Revolt? JAMA Intern Med. 2016;176(11):1599-1600.
- 12. Norman G, Norcini J, Bordage G. Competency-based education: milestones or millstones? J Grad Med Educ. 2014 Mar;6(1):1-6
- 13. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and evaluating complex interventions: the new Medical Research Council guidance. BMJ. 2008 29;337(sep29 1):a1655–a1655.
- 14. Holmboe ES, Call S, Ficalora RD. Milestones and Competency-Based Medical Education in Internal Medicine. JAMA Intern Med. 2016;176(11):1601-1602
- 15. Pawson R, Greenhalgh T, Harvey G, Walshe K. 2005. Realist review A new method of systematic review designed for complex policy interventions. J Health Serv Res Policy 10(Suppl. 1):21–34.
- 16. Ericsson KA. Deliberate practice and the acquisition and maintenance of expert performance in medicine and related domains. Acad Med. 2004;79(10 Suppl):S70-81.
- 17. Nelson EC, Batalden PB, Godfrey MM. Quality by Design. A Clinical Microsystems Approach. Jossey-Bass. San Francisco. 2007.
- 18. Nasca TJ, Philibert I, Brigham T, Flynn TC. The next GME accreditation system--rationale and benefits. N Engl J Med. 2012 Mar 15;366(11):1051-6.