How reliable is online diffusion of medical information targeting patients and families?

Pedro Xavier-Elsas, Sandra Epifânio Bastos, Maria Ignez C Gaspar-Elsas

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**Correspondence to:** Pedro Xavier-Elsas, MD, PhD, Associate Professor, Department of Immunology, Instituto de Microbiologia Prof. Paulo de Góes, Universidade Federal do Rio de Janeiro (UFRJ), CCS, Bloco I, Room 1-2-066, Rio de Janeiro, CEP 21941-590, Brazil. pxelsas@micro.ufrj.br

**Telephone:** +55-21-25608344-162

**Fax:** +55-21-25608344

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**Abstract**

**AIM:** To determine whether online diffusion of the "Ten Warning Signs of Primary Immunodeficiency Diseases (PID)" adheres to accepted scientific standards.

**METHODS:** We analyzed how reproducible is online diffusion of a unique instrument, the "Ten Warning Signs of PID", created by the Jeffrey Modell Foundation (JMF), by Google-assisted searches among highly visited sites from professional, academic and scientific organizations; governmental agencies; and patient support/advocacy organizations. We examined the diffusion, consistency of use and adequate referencing of this instrument. Where applicable, variant versions of the instrument were examined for changes in factual content that would have practical impact on physicians or on patients and their families.

**RESULTS:** Among the first 100 sites identified by Google search, 85 faithfully reproduced the JMF model, and correctly referenced to its source. By contrast, the other 15 also referenced the JMF source but presented one or more changes in content relative to their purported model and therefore represent uncontrolled variants, of unknown origin. Discrepancies identified in the latter included changes in factual content of the original JMF list (C), as well as removal (R) and introduction (I) of novel signs (Table 2), all made without reference to any scientific publications that might account for the drastic changes in factual content. Factual changes include changes in...
the number of infectious episodes considered necessary to raise suspicion of PID, as well as the inclusion of various medical conditions not mentioned in the original. Together, these changes will affect the way physicians use the instrument to consult or to inform patients, and the way patients and families think about the need for specialist consultation in view of a possible PID diagnosis.

CONCLUSION: The retrieved adaptations and variants, which significantly depart from the original instrument, raise concerns about standards for scientific information provided online to physicians, patients and families.

Key words: Information technology and human health; Expert consultation online; Online medical information; Warning signs; Infection; Diagnosis

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Core tip: We analyzed how reproducible is online diffusion of a unique instrument, the “Ten Warning Signs of Primary Immunodeficiency Diseases”, to define whether information made available to physicians, families and support/advocacy groups through the internet adheres to accepted scientific standards. The results show that this instrument is diffused through many sites, but the actual scientific contents often depart substantially from their purported model. This raises concerns about the quality of scientific information provided online on medical matters, and on the need for corrective mechanisms in an age when the public is increasingly dependent on the internet as primary source of knowledge.

INTRODUCTION

The personal computer and access to the Internet have affected medicine as rarely seen with previous technological advances, due to the large-scale inclusion of patients, families and support/advocacy groups as a highly motivated audience. Emerging online resources for communication, diffusion and education in the medical sciences profoundly changed the way physicians and patients view the possible diagnosis of uncommon, chronic disease, and the prospects for long and complex evaluation procedures. The Internet is now a major source of information on all aspects of medical science, which is consulted routinely by doctors worldwide. Many laymen also consult the Internet about rare, incapacitating diseases, and make decisions on the basis of factual information retrieved through Google and similar search tools. For families, this often means deciding for, or against, further search for specialty physicians and reference centers. Hence, online information must be consistent in itself, and based on best standards for scientific evidence, both in its initial presentation and in subsequent revised versions (whenever these are prompted by advances in medical knowledge). Deviance from this course will likely increase the risk of misinforming the public, entailing unpredictable risks for patients and their families.

The field of primary immunodeficiency diseases (PID) is a rapidly evolving area of medical science in which the advantages of diffusing medical information online are easy to grasp. PID[1] are a group of chronic, complex diseases[2] which poses a unique public health problem, because: (1) as a group, they are rare, but present worldwide; (2) they are biologically complex and very heterogeneous[3,4], but nevertheless share a set of major outcomes (increased susceptibility to repeated and/or opportunistic infections, autoimmunity and malignancy) which predispose to increased mortality and/or severe complications and sequelae[5]; (3) they arise in congenital defects of the immune system, which often lead to clinical deficiencies in infancy and childhood, and unless corrected through costly and technically complex procedures, may have a major impact on the growth and development, as well as socialization and schooling of the child[1,4]; and (4) they have a genetic basis that accounts for family clustering of cases, thereby making accurate diagnosis and increased awareness among health professionals indispensable for adequate family counseling[1-4].

In short, although PID patients must be managed by highly specialized professional teams, they mostly come from environments which lack specialists, and further lack the information about PID that would prompt families and primary care physicians to seek for specialists’ counsel. Together, this creates the need for mechanisms to bring together the demographically rare, geographically dispersed and clinically heterogeneous patient population, on the one hand, and the institutionally rare, geographically concentrated and technologically demanding specialist population, on the other hand. This task can be made easier by letting the patients, their families and their primary care physicians know that they need the type of specialized care which is not available everywhere, but at specific tertiary institutions to which they can be referred. This challenge has been met by the Jeffrey Modell Foundation (JMF) through the elaboration of a list of Ten Warning Signs of Primary Immunodeficiency (hereafter referred to as “the JMF list”), to be diffused among patients and their families, primary care physicians and the general public, to raise awareness that certain clinical manifestations reflect an underlying PID that needs diagnostic workout. The creation of the JMF list has merit in itself, but its usefulness depends on whether it is scientifically accurate and correctly referenced, wherever it is found.
online. Because this well-structured and authoritative text provides an ideal probe to examine whether medical information can be propagated online risk-free, we addressed here the online diffusion of the scientific information it embodies, as well as the emergence of variants that may appear in this process. The results show that the “Ten warning signs of primary immune deficiency” are quite suitable for an object-lesson on the fate of scientific information in the Cyberage.

MATERIALS AND METHODS

Study design
Initial evaluation of the frequency, extent and types of variation among online sites in the contents and referencing of the JMF list was carried out in the 100 most accessed web pages identified by Google with search term Ten warning signs of Primary Immune Deficiency (search date April 23, 2012). This was done to approximate as much as possible the most frequent situation, namely that in which someone tries, for the first time, to learn something about the Ten Warning Signs of PID online. To further assess the diffusion, accuracy of citation and consistency of use of the JMF list online, we examined in detail sites from: (1) professional, academic and scientific organizations, including, but not limited to, International Union of Immunological Societies, European Society of Immunodeficiencies, Sociedade Brasileira de Imunologia, Associação Brasileira de Alergia e Imunopatologia; (2) governmental agencies, including CDC and NIH; and (3) patient support organizations, including JMF and BRAGID (Grupo Brasileiro de Imunodeficiência).

Definition of terms
For the purposes of this study: (1) the concept is defined here as any list of Warning signs of PID, to be diffused among the nonspecialist public, regardless of whether it derives from the original JMF list; (2) the application of this Concept refers to the creation and use of any list of Warning signs of PID, which could be retrieved in our search; (3) referencing refers to the acknowledgement, by any given site applying the Concept, that it is aware of the JMF site (usually embodied in a link to the JMF site), or that JMF is considered a valid source of information on PID, regardless of whether the Concept as development in the site are actually related to the JMF list (i.e., correct referencing) or not (incorrect referencing). Referencing, correct or incorrect, demonstrates that the site applying the Concept derives a measure of scientific credibility from acknowledging JMF as the referred source; and (4) variation refers to any departure in structure, language, or factual content (including quantitative information), from the original JMF list, which is accessible at the JMF site (www.jmfworld.com).

On the other hand, any variant list retrievable by the search tool could also originate in a completely independent source, unrelated to JMF, and in this case would represent an independent application of the Concept. If such a hypothetical alternative source were properly referenced, the application would not be included in our study as an undue variation of the JMF model. In our study, however (see results and discussion), both preserved and variant versions of the JMF list, some of the latter strikingly different from the JMF original, were all referenced to the JMF site.

Identification and classification of variants
Variation was considered significant if: (1) information contained in the original was removed (R), or changed (C) in factual/quantitative content so as to be of practical consequence; (2) information not contained in the original was introduced (I); and (3) information contained in the original was rearranged (displaced in its original context), or generalized (absorbed into a more comprehensive class not explicitly mentioned in the original) so as to change (C) the interpretation of the conveyed message. Deletion or addition of signs represents extreme examples of removal and introduction, respectively. A significant variant may differ from the standard in one or more signs, and therefore one significant change is sufficient to define a variant. On the other hand, preservation (P) of the original content is defined as complete identity of content between any given variant and the JMF list, and therefore precludes any significant change of content. Accordingly, less significant, or nonsignificant, variation, such as a change in language that did not affect the factual information, or a change in the order in which the warning signs were listed, was also found in our study, but was not further discussed below, to help us focus on discussing consequential issues.

The frequency of variation is defined as the ratio between the number of variant versions and the number of total versions sampled. The extent of variation (i.e., the degree to which any given version differs from the purported original) found, as well as the types of variation detected (removal, introduction, change of content), can be found in the accompanying lists of sites which faithfully reproduce the JMF list (Table 1) and of variations found in those that do not (Table 2). For the extreme forms of introduction, which result in addition of novel signs, amounting to a drastic change in content, we further recorded the number of novel signs added to the original JMF material.

RESULTS
Preservation/change of the original message among highly accessed pages. Although numerous online information sources nominally refer to the JMF list, not every site consulted shows complete P of JMF original contents. The majority of pages faithfully reproduce the original information (Table 1), and are representative of adequate online sources of medical information (out of 48, 10 were from pharmaceutical companies; 21 from patient support groups focusing on severe and
chronic conditions; 4 mirrored the JMF site; 5 were from hospitals; 1 from an elementary school; 2 from NIH; 1 from an university; 1 from a scientific society; 3 reviewed a book on PID). Nevertheless, we found a sizeable minority (15 out of the 100 most highly accessed sites identified by Google) that displayed lists departing substantially from their purported model (Table 2). Discrepancies identified in the latter included changes in factual content of the original JMF list (C), as well as removal (R) and introduction (I) of novel signs (Table 2), all made without reference to any scientific publications that might account for the drastic changes in factual content.

Incorrect referencing in variant pages

Importantly, 14 of these 15 variant lists directly refer to the original JMF (direct links), or to sites with links to JMF (indirect links), as their source, and therefore represents undisputable examples of incorrect referencing, an unacceptable practice by current standards of scientific communication. Importantly, the variant versions include some sponsored by professional societies, governmental regulatory and research agencies, and respected biomedical research institutes, which thereby lend authority to an online resource that fails to meet standards of citation and referencing.

Major departures from the JMF list

Among the top 100 pages identified by Google, 3 formed a set with similar content, which departed strikingly from the JMF list. This included 1 page associated with the Mayo Clinic (http://www.mayoclinic.com/health/primary-immunodeficiency/DS01006), and 2 pages associated with www.livestrong.com (www.
Table 2  Variant versions of the Jeffrey Modell Foundation list in the first 100 pages retrieved by Google

| Site consulted | 10 warning signs of primary immunodeficiency of the Jeffrey Modell Foundation | 1 | JMF |
|---------------|---------------------------------------------------------------------------------|---|---|
| a             | C P P P P P P C P C P N 0 N N                                               |   |   |
| b             | C P P R P P P C P C P N 0 Y N                                               |   |   |
| c             | C C C R P C C R R R C Y 4 N Y                                               |   |   |
| d             | C P P P P P C C P P N 0 Y N                                               |   |   |
| e             | C P P P C P C P C P N 0 Y N                                               |   |   |
| f             | C P P C P C C C P C P N 0 Y N                                               |   |   |
| g             | C C P P P C C R C P Y 1 N Y                                               |   |   |
| h             | C P R P P P C C C P Y 4 Y N                                               |   |   |
| i             | C P P P P C C C C N 0 N Y                                               |   |   |
| j             | C P R P P P C P C P Y 4 Y N                                               |   |   |
| k             | C P P P P P C C C P N 0 Y N                                               |   |   |
| l             | C P P P P P C C C P N 0 N Y                                               |   |   |
| m             | C P P P P P C C C P N 0 Y N                                               |   |   |
| n             | C P P P P P C C C P N 0 N Y                                               |   |   |
| o             | C P P P P P C C C C N 0 Y N                                               |   |   |

1 http://www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=warningsigns;  2 http://www.stopgettingsick.com/template.cfm-1685;  3 http://www.aafp.org/afp/2003/1115/p2011.html;  4 http://www.livestrong.com/article/71656-top-ten-warning-signs-primary/;  5 http://docphyl.com/index.php?page=pages/pimmunodeficiency;  6 http://ezinearticles.com/?10-Warning-Signs-of-Primary-Immunodeficiency&id=1297957;  7 http://www.momlogic.com/resources/primary_immunodeficiency_diseases.php;  8 http://www.irishhealth.com/article.html?id=3927;  9 http://www.aefat.es/docs/immunodefprim_aafp.pdf;  10 www.bpl.co.uk/...primary-immunodeficiency/39;  11 http://www.aafp.org/afp/2003/1115/p2001.html;  12 http://www.insidetoronto.com/insidetoronto/article/57439;  13 http://www.allergyconsumerreview.com/sinus-infection.html;  14 http://www.aacijournal.com/content/7/S1/S11;  15 http://begunnybag.files.wordpress.com/.../primary-im;  16 http://www.nichd.nih.gov/health/topics/primary_immunodeficiency.cfm;  17 Preserved;  R: Removed;  I: Introduced;  C: Changed content; n: Number of novel signs introduced. Search verified 04/23/2012.

livestrong.com/article/71656-top-ten-warning-signs-primary/; and www.livestrong.com/article/253355-10-signs-of-primary-immunodeficiency/), which presents itself as based on the Mayo Clinic. In this particular example, the key message was profoundly altered, but presented no support of scientific evidence to justify these changes. It also included a series of explanatory notes in language accessible to the nonmedical public, which represents a further departure from the language in which the JMF original is cast, of obvious consequence for the impact on families and patients, regardless of whether it is scientifically accurate. This specific example, which is of undeniable relevance, given the high number of accesses, as well as the high scientific profile of the sponsoring institution, and the wider audience presumably intended, illustrates the hazards of uncontrolled diffusion of medical information online.

**Variation is not un consequential**

Scientific information was changed in some variant versions so as to have the potential for undesirable consequences in medical practice. A clear example follows: The "Four or more new ear infections within 1 year" of the JMF list were changed into "Eight or more new ear infections within 1 year" in several sites (The American Academy of Family Physicians; University of Wisconsin; the http://www.stopgettingsick.com/template.cfm-1685 patient support site; The Australasian Society of Clinical Immunology and Allergy/ASCIA). In the Mayo Clinic-related sites mentioned above, the same original content was generalized to "Frequent/recurrent infections". In the first case, a patient who would previously be considered worthy of evaluation for PID (according to the JMF list) must now suffer twice as many ear infections before qualifying as a candidate for PID evaluation. In the second case, the criteria became so broad as to lose their usefulness, for the definition would equally well apply to the numerous people living in conditions of poor hygiene and sanitation worldwide, who have no PID. The fate of the patient will therefore hinge on which version of the list has been consulted by the physician, an issue with broader implications for the rights of patients to appropriate medical attention.

A further example of generalization is provided by the Mayo Clinic, which introduced in their list of warning signs the following: inflammation and infection in internal organs, including the liver; autoimmune disorders, such as Lupus erythematosus, arthritis or type I diabetes; hematological disorders, such as low platelet counts and anemias; digestive problems, including cramps, loss of apetite, nausea and diarrhea; and delayed growth and development. Considering the high frequency with which any of the preceding occurs in the absence of PID, it is open to question whether such comprehensive enumeration of "warning signs for PID" will benefit patients and improve the physician’s capabilities to deal with PID.

**Local adaptations - is PID the same everywhere?**

A different, but related, finding points to the adaptation of the original model to regional peculiarities. A very good example of adaptation is offered by BRAGID (Brazilian Group for Immune Deficiency), a patient-support organization. Although the BRAGID site (www.
imunopediatria.org.br) is not within the top 100 sites identified by Google, and therefore was not included in Table 2, it is here analyzed in detail because it plays a very important role in Brazil, where other sources of information on PID are scarce. The list accessed through BRAGID includes: “repeated intestinal infections, chronic diarrhea, severe asthma, collagen (autoimmune) diseases, adverse effects of BCG (tuberculosis) vaccination, mycobacterial infections, and a clinical phenotype suggestive of immune deficiency” (an odd item in a list directed to a public supposed to know little about immune deficiency and even less about the associated clinical phenotypes).

This adaptation likely reflects an effort to increase the usefulness of the concept to a developing country, where exposure to the mycobacteria that causes tuberculosis remains very important. The reference to adverse effects of BCG vaccination is equally appropriate to this context, since this is not a universally enforced practice, but is very relevant to Brazil as well as to PID patients[8-10]. However, the spectrum of clinical conditions enumerated includes repeated intestinal infections, chronic diarrhea, severe asthma and autoimmune diseases. This is less likely to help, as in a developing country such as Brazil infectious pathogens and environmental pollutants are major contributing factors for intestinal infection, chronic diarrhea, severe asthma, and even autoimmune manifestations in endemic diseases, which far outweigh their possible contribution to PID detection and management. As an effort of regional adaptation is to be commended, when justified by local factors, one should never omit the fact that this is an evolution from the original concept of signs of PID; by consequence, referencing to a well-established model without recording that it is a modification counters standard practice.

**DISCUSSION**

**Anonymous expertise in an age of evidence-based medicine**

It is surprising that factual content that informs medical decisions and medical education could undergo such uncontrolled variation online, especially in an age that stresses the importance of rigorous scientific documentation for sound medical practice. The fate of the JMF list online should raise concern in clinicians and scientists alike, because this unexplained variance in factual content counters basic rules in scientific communication, as significant changes in content were made without justification or references, and no responsibility was taken for them. Through incorrect referencing to the original from which they depart, variant lists are further misleading both physicians and patients as to the scientific basis of their content, and evading accountability for the possible untoward consequences of disseminating inaccurate information. Such attitude is common in many dimensions of the Cyberspace, since any private citizen with access to the Internet can upload content for all to view and download elsewhere, no matter how idiosyncratic or absurd this content may be. In domains other than medical science, the cover of anonymity also facilitates the dissemination of opinions that would probably be held back, if the author could easily be made accountable for them. Curiously, this sharply contrasts with the traditional environment in medical science, where authors typically identify themselves to the public, and highlight their professional qualifications and experience when delivering expert opinion, while referees tend to be covered by anonymity, although they act as guardians of scientific standards of originality, veracity and accountability. In an age of democratic online publishing, the provision of arbitrary, anonymous views as innocent “variations” of somebody else’s better-known work does not further the cause of evidence-based medicine.

**Academic freedom, scientific accountability and public trust**

The JMF list of warning signs, like any scientific document, is perfectable and even open to challenge, a particularly timely issue, as illustrated by recent publications[8-10]. This work does not address the validity of the original list, but to show that it did not undergo online diffusion without a significant amount of distortion, adaptation or modification. Our intent is to highlight the potential presented by the Internet for distortion or corruption of factual information when nobody is paying attention to what is being diffused, and to who takes responsibility for the modifications.

While we concede that online medical information should be subject to no censorship, it is not sound science to advance a dissenting opinion which has neither an identifiable author nor a peer-reviewed reference. Academic freedom allows anyone to create his/her own list of warning signs of PID, or to modify an existing one if it is understood to be outdated. In the field of immunological diseases, which includes PID, a time-honored classification by Gell and Coombs has recently been revised in-depth, on the basis of extensive scientific evidence[11]. The latter revision was certainly not an anonymous document, nor lacked references to back it. By the same token, those willing to do so for lists of PID signs should take responsibility for the changes made, in addition to acknowledging their indebtedness to the original they improved upon, rather than attributing their own views to the JMF through incorrect referencing. The confidence of the public in medical information diffused online could only increase if unjustified changes to this information were reported to the original source, thereby promoting sound practices and scientific accountability.

We hope this examination of a strictly defined issue (variations of content in a single piece of medical information), which is highly appropriate as an object for study, but relevant to a relatively small number of people worldwide, will prompt others, better qualified
than ourselves, to extend our initial probing to broader areas, where issues may be manifold and potentially relevant to public health in a larger scale. Among the most interesting and timely subjects for such a broadened examination, we would suggest online resources focusing on other diseases such as AIDS and tuberculosis, which, like PID, involve issues of increased susceptibility to infection, but have far greater social impact, due to the number of affected subjects worldwide.

COMMENTS

Background

Information technology and the Internet have profoundly changed the way physicians, patients, families and support/advocacy groups access and handle information on diseases, diagnoses, and novel/experimental treatments, but it remains unclear whether this revolutionary change adheres to accepted scientific standards of reliability, accuracy and referencing. The authors analyzed how reproducible is online diffusion of a unique instrument, the "Ten Warning Signs of primary immunodeficiency diseases (PID)''. This was done because: (1) PID are a large and heterogeneous group of diseases, with related but distinct mechanisms, variable clinical presentations and complex therapeutic choices, requiring specialized diagnostic tools and expert counseling, not necessarily available in general hospitals and clinics; (2) the rarity of most varieties of PID, and the geographical concentration of the diagnostic and therapeutic resources, highlight the practical value of bringing together PID specialists and prospective patients through information diffused online; and (3) this instrument is clearly and concisely written, providing accurate, well-organized and useful information, therefore unreliable diffusion of its contents would have, in practice, a negative effect on the quality of information provided online.

Research frontiers

Although most people wouldn’t think of the personal computer and the internet as advanced medical technology, they are fully integrated into medical practice in most countries, and the public, including doctors, trusts them to make important decisions. Nevertheless, there is no systematic follow-up of the contents of medical information pieces propagated in the internet. This is difficult to do in most cases, because large pieces of information on the same subjects would have to be compared, and there are many pieces to compare. In the authors’ case, this examination is made easy, because the authors followed a very small piece of factual information up, which is well-structured and divided in numbered statements, so that comparison between the original and any variants is facilitated. This approach allowed the authors to examine, for the first time, the issue of uncontrolled fakes for medical information online, and to evaluate the extent of the resulting distortions.

Innovations and breakthroughs

What is novel in the study is that, by examining the diffusion, consistency of use and adequate referencing of this instrument, among highly visited sites from professional, academic and scientific organizations, governmental agencies and patient support/advocacy organizations, the authors could show that the actual contents displayed often depart substantially from their purported model, in form and factual content, including unjustified eliminations and additions. In short, in a sizable proportion of cases, information is deleted, distorted or corrupted, but these changes go unnoticed or unreported.

Applications

The study shows that, by the appropriate choice of a piece of information to be monitored, it is possible to determine how well it adheres to accepted standards of scientific communication, which is central to its credibility and practical usefulness. This strategy should be applicable to other areas of Medicine affecting large numbers of people, as for instance those concerned by tuberculosis, AIDS or the benefits and risks of vaccination.

Terminology

PID are a large number of different diseases of variable clinical presentation and severity, and demanding specialized diagnosis and management which is not available everywhere. Due to their similarities in mechanisms and manifestations, PID as a group is associated with a constellation of clinical signs and symptoms, mostly due to a higher frequency of infection. The “Ten Warning Signs of PID’’ is short list of such signs and symptoms, intended to help families to decide whether or not a given patient should be evaluated for PID.

Peer-review

The authors have picked a usual yet interesting and important question regarding the diffusion of medical information in the cyberspace.

REFERENCES

1 Notarangelo LD, Fischer A, Geha RS, Casanova JL, Chapel H, Conley ME, Cunningham-Rundles C, Etzioni A, Hammartrom L, Nonoyama S, Ochs HD, Puck J, Roffman C, Seger R, Wedgwood J. Primary immunodeficiencies: 2009 update. J Allergy Clin Immunol 2009; 124: 1161-1178 [PMID: 20004777 DOI: 10.1016/j.jaci.2009.10.013]
2 Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson RP, Orange JS, Routes JM, Shearer WT, Sorenson RU. Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005; 94: S1-63 [PMID: 15945566]
3 Savides C, Shaker M. More than just infections: an update on primary immune deficiencies. Curr Opin Pediatr 2010; 22: 647-654 [PMID: 20683329 DOI: 10.1097/MOP.0b013e32833dd286]
4 Turvey SE, Bonilla FA, Junker AK. Primary immunodeficiency diseases: a practical guide for clinicians. Postgrad Med J 2009; 85: 660-666 [PMID: 20075404 DOI: 10.1136/pgmj.2009.080860]
5 Dara M, Acosta CD, Rusovich V, Zellweger JP, Centis R, Migliori GB. Bacille Calmette-Guérin vaccination: the current situation in Europe. Eur Respir J 2014; 43: 24-35 [PMID: 24381321 DOI: 10.1183/09031936.00134113]
6 Haile M, Källenius G. Recent developments in tuberculosis vaccines. Curr Opin Infect Dis 2005; 18: 211-215 [PMID: 15864007]
7 Hesseling AC, Cotton MF, Fordham van Rey C, Graham SM, Gie RP, Hussey GD. Consensus statement on the revised World Health Organization recommendations for BCG vaccination in HIV-infected infants. Int J Tuberc Lung Dis 2008; 12: 1376-1379 [PMID: 19017445]
8 Arkwright PD, Gennery AR. Ten warning signs of primary immunodeficiency: a new paradigm is needed for the 21st century. Ann N Y Acad Sci 2011; 1238: 7-14 [PMID: 22129048 DOI: 10.1111/j.1749-6632.2011.06206.x]
9 Subbarayan A, Colarsusso G, Hughes SM, Gennery AR, Slater M, Cant AJ, Arkwright PD. Clinical features that identify children with primary immunodeficiency diseases. Pediatrics 2011; 127: 810-816 [PMID: 21482601 DOI: 10.1542/peds.2010-3680]
10 MacGninette A, Aloi F, Mishra S. Clinical characteristics of pediatric patients evaluated for primary immunodeficiency. Pediatr Allergy Immunol 2011; 22: 671-675 [PMID: 21449988 DOI: 10.1111/j.1399-3038.2011.01167.x]
11 Descotes J, Choquet-Kastylevsky G. Gill and Coombs’s classification: is it still valid? Toxicology 2001; 158: 43-49 [PMID: 11164991]
