Retinoblastoma genetics in India: From research to implementation

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Retinoblastoma is the prototypic genetic cancer. India carries the biggest burden of retinoblastoma globally, with an estimated 1500 new cases annually. Recent advances in retinoblastoma genetics are reviewed, focusing specifically on information with clinical significance to patients. The Indian literature on retinoblastoma clinical genetics is also highlighted, with a comment on challenges and future directions. The review concludes with recommendations to help clinicians implement and translate retinoblastoma genetics to their practice.

Key words: India, genetics, retinoblastoma, review

Introduction

As the first tumor to be confirmed to have genetic origins,[¹⁻³] the study of retinoblastoma has contributed much to our understanding of heritability of cancer. While most of the genetic research aims to elucidate the precise molecular development of the disease, there are important discoveries that can be applied directly to patient care and improve lives.

An estimated 20% of the world’s retinoblastoma patients live in India. This has great implications for India’s healthcare system, not only in the burden it creates, but the opportunities that emerge for the health and research.

This review article has two main aims. First, it reviews advances in retinoblastoma genetics, specifically focusing on information that is currently relevant and applicable to patient care. Second, it presents a scoping review aimed at determining the breadth and depth of retinoblastoma clinical genetic work in India. The review article concludes with recommendations to help healthcare workers implement and translate retinoblastoma genetics in their clinic so that Indian families affected with retinoblastoma can benefit from the most up-to-date relevant science.

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Manuscript received: 30.10.14; Revision accepted: 08.04.15

Methods

Search strategy 1

Review of retinoblastoma clinical genetics

To inform the first part of this review, a search of PubMed (accessed January 15, 2014) was performed to identify relevant and timely articles. Key words included “retinoblastoma genetics,” “RB1 gene,” “retinoblastoma genetic testing,” and “retinoblastoma genetics counseling.” Additional reviews on retinoblastoma and retinoblastoma genetics were identified by hand-searching.

Search strategy 2

Scoping review of Indian retinoblastoma clinical genetics

To inform the second part of this review article, PubMed was searched (January 15, 2014) for all articles that listed “retinoblastoma” as a key word and “India” as an affiliation. Results of the search were exported as a comma separated value (.csv) file and analyzed using Microsoft Excel.

Study selection, inclusion and exclusion criteria

Papers that did not explicitly focus on retinoblastoma were excluded. Papers were coded as “Clinical” (primary research on patients and/or patient outcomes), “Basic” (primary research relating to biological mechanisms of retinoblastoma), “Genetic” (primary research relating to retinoblastoma medical genetics/mutation detection) or “Review” (nonprimary research, review articles). A Google Search with the terms “retinoblastoma genetics in India” was also performed (January 21, 2014), in order to locate additional clinical genetics papers that might have been missed in the PubMed search.

Data extraction and analysis

Where provided, data were extracted from clinical genetics papers to calculate the sensitivity of RB1 mutation testing...
for unilateral (UNI) and bilateral (BI) cases. This information included: Number of patients reported on, laterality, number of blood specimens tested (BI), number of M1 mutations found (BI), number of tumor specimens tested (UNI), number of M1/M2 pairs of mutations found (UNI).

**Retinoblastoma genetics: An overview**

Genetic origins and heritability of retinoblastoma

Retinoblastoma was the first tumor in which the genetic nature of cancer was revealed.\(^1\)\(^-\)\(^5\) Even though all retinoblastoma tumors are caused by genetic aberrations, this does not mean that all patients have inherited the disease, nor does it mean that all cases are inheritable by the next generation. More recent studies also show us that retinoblastoma tumors may differ in the mutagenic pathway they take from normal to malignant cell; for example, some retinoblastoma tumors are caused by RB1 mutation\(^6\)\(^-\)\(^9\) and others by amplification of the MYCN gene.\(^6\) To understand retinoblastoma genetics, it is helpful to think of the disease in terms of heritability (heritable or nonheritable) and laterality (UNI or BI).

Individuals with heritable retinoblastoma (48%) carry a germline mutation in the RB1 tumor suppressor gene, and are predisposed to developing not just retinal tumors (UNI, 7%, or BI, 40%), but also pineal tumors (trilateral) and second cancers later in life. The majority of heritable retinoblastoma patients will develop retinal tumors, either benign (retinoma) or malignant (retinoblastoma) both caused by loss of the second RB1 allele in a susceptible retinal cell. However, it is also possible to have heritable retinoblastoma and develop no retinal tumors (1%); these individuals are still at risk for cancers later in life [Fig. 1].\(^7\)

Approximately, 10% of individuals with heritable retinoblastoma will have inherited the RB1 mutation from a parent. This means the majority of individuals with heritable retinoblastoma are the first affected person in their family.

Approximately, 4% of individuals with heritable retinoblastoma are mosaic for the RB1 mutation, meaning that the mutation occurred during embryogenesis and affects a fraction of the total germline.\(^8\)\(^-\)\(^9\) Mosaic individuals could not have inherited their mutation (otherwise they would carry the RB1 mutation in all of their cells) but their disease could be inheritable by the next generation. Arguably, mosaicism may reduce the risk of transmission for the next generation; however, there exist no reliable data at the moment to be able to accurately calculate potential reduced risks.

Individuals with nonheritable retinoblastoma (52%) have normal RB1 genes at the germline level. Tumors are always UNI and unilateral, and develop in one of two ways: (1) Loss of both copies of RB1 in a susceptible retinal cell (51%), or (2) amplification of the MYCN oncogene in a susceptible retinal cell (1%). Since the genetic aberrations are somatic, these individuals are not at increased risk for cancers later in life, nor are any of their relatives, present or future.\(^7\)

**Genetic progression of retinoblastoma**

For the majority of retinoblastoma tumors, the loss of two RB1 alleles in a susceptible retinal cell induces genomic instability that leads to copy number alterations in several other genes: Copy number gains in MDM4, KIF14, MYCN, DEK, and E2F3, as well as loss of CDH11.\(^10\) The relative degree of gains and losses distinguishes benign retinoma (less genomic instability) from malignant retinoblastoma (more genomic instability).\(^11\) Additional genetic alterations during the development of retinoblastoma include deregulation of microRNAs, aberrant methylations, single nucleotide polymorphisms, and differential gene expression; these have been comprehensively reviewed elsewhere.\(^12\)

Less is known about the development of the MYCN\(^{\text{amp}}\) tumors beyond the initiating amplification of the MYCN oncogene.\(^6\) Is MYCN amplification the only genomic event driving malignancy of these tumors? Do MYCN\(^{\text{amp}}\) tumors have a different cell of origin than RB1\(^{−/−}\) retinoblastomas? These questions remain to be answered, and further study is required.

**Retinoblastoma genetic testing and counseling**

With respect to the retinoblastoma patient, while research into the genetic progression of retinoblastoma beyond the initiating mutational event may one day lead to targeted therapies, today, very little of this work is relevant to clinical care. Instead, it is imperative to know whether or not they have heritable retinoblastoma; additional information on the identity of the initiating event can then be used to direct care. For example, it is obvious that all BI patients have heritable retinoblastoma, however, without genetic testing to discover the identity of the RB1 mutation, precise prediction of risk in family members and future offspring is not possible. This becomes even more important for UNI patients, where precise genetic detection can differentiate between heritable and nonheritable cases, and RB1\(^{−/−}\) versus MYCN\(^{\text{amp}}\) retinoblastoma.

Knowledge of the molecular genetic make-up of retinoblastoma tumors and an individual’s mutation carrier status makes surveillance and treatment of the patient and related families possible, while elimination of this risk excludes individuals from unnecessary hospital visits and worry. For this to happen, two tools are important: Comprehensive genetic testing by a capable lab and sensitive and accurate counseling to relay the information to the patient and family.

**Retinoblastoma genetic testing**

The discovery and interpretation of the genetic result are only as good as the technique that precedes it. This starts from the point of the sample (blood and/or tumor) collection. This is particularly important for tumor, which unlike blood, can only be sampled once: after enucleation and before the rest of the eye is sent to histopathology. A protocol has been suggested to optimize tumor collection for genetics while maintaining the integrity of the specimen for subsequent histopathological analysis.\(^13\) The choice of storage media is important so as to ensure optimal extraction of DNA, and possibly RNA. Laboratories that specialize in retinoblastoma genetics can advise on the optimal collection, storage and transport procedures for both tumor and blood.

**RB1 testing**

Virtually, every new retinoblastoma patient will display a unique RB1 mutation (excluding of course, those who have MYCN\(^{\text{amp}}\) retinoblastoma).\(^14\)\(^15\) Very few RB1 mutations are recurrent. This means that genetic testing in the proband is always a journey of discovery, rather than a simple screen for known mutations. The RB1 gene can be damaged in a
myriad of ways, including large and small deletions, point mutations, insertions, translocations, deep intronic splice mutations, and promoter methylation.\textsuperscript{[14,15]} This means many different techniques must be used in the search of the offending mutation.\textsuperscript{[15-17]} However, once the exact mutation is identified in the proband, then relatives and future offspring can be screened quite easily for the known mutation.

**Test sensitivity**

There are several laboratories around the world that offer retinoblastoma genetic testing services, ranging from fully certified commercial diagnostic labs to basic science research labs. Test sensitivity can be one way to distinguish how reliable the results are from any one of these laboratories.

Test sensitivity is calculated separately for UNI and BI cases, using a simple formula:

\[
\text{Bilateral Sensitivity} = \frac{\text{No. of germline mutations found (blood)}}{\text{No. of probands tested}}
\]

\[
\text{Unilateral Sensitivity} = \frac{\text{No. of both mutations found (tumor)}}{\text{No. of probands tested}}
\]

Note that for both formulas, we know that the maximum possible outcome is 100%. That is to say, it is known that 100% of BI patients carry a germline \(RB1\) mutation in the blood; also, it is known that 100% of UNI patients (save for \(MYCN\) amp cases) will have mutations in both tumor \(RB1\) alleles.

This is not to say laboratories should be expected to reach 100% sensitivity. That may well be impossible with currently available methods and technologies. However, the degree of deviation from 100% sensitivity can be used to gauge how well a given laboratory performs in detecting expected \(RB1\) mutations.

Test sensitivity is an important factor in interpreting a “no mutation found” result. How can one know if a “no mutation found” result is due to limitations of the lab to detect an existing mutation, or if the person being tested is actually not a mutation carrier?

Consider a UNI patient with no family history. Without genetic testing to confirm or eliminate the possibility that this is heritable retinoblastoma, the physician must continue to examine that child in case they develop tumors in the unaffected eye. The child’s family members must also be presumed to be at risk.

Now, imagine that the tumor and blood of that child are tested. In the best case scenario, two \(RB1\) mutations are found in the tumor and then screened for in the blood to determine if the child has heritable (one of the two tumor \(RB1\) mutations is detected in the blood) or nonheritable retinoblastoma (none of the two tumor \(RB1\) mutations is detected in the blood).
Alternatively, imagine that the laboratory is sent only a blood sample because the physician has chosen to treat the affected eye (thus no tumor sample is available). The blood sample is tested, but no mutation is found. Is the child truly a nonheritable case, or has the laboratory failed to detect an existing germline RB1 mutation?

One recommendation that has emerged from the Canadian Guidelines for Retinoblastoma Care states “as long as the laboratory has demonstrated, that 90% of RB1 mutations can be identified, a negative result means risks are low enough that examinations under anaesthesia can be avoided.”[18] Further to this, the number of tumors a given lab has tested also plays a role in interpreting sensitivity. A high sensitivity with very few specimens ever tested is not reliable, in the same way that many specimens tested with a low sensitivity points to limited ability to reliably detect RB1 mutations. The highest reported sensitivity for RB1 mutation testing is 96%.[9]

**MYCN**<sup>amp</sup> detection

The discovery of MYCN<sup>amp</sup> retinoblastoma is relatively new.[4] A relatively simple copy number test of tumor DNA for the MYCN gene can detect this form or retinoblastoma quite easily. Because of its rarity, it makes sense that this test would be performed after genetic testing for RB1 failed to reveal a mutation in a UNI tumor, or if histology first revealed presence of neuroblastoma-like histology, a distinctive feature of MYCN<sup>amp</sup> retinoblastoma.

Molecular metastatic surveillance

The molecular signature of retinoblastoma tumors can be used to develop individualized genetic screens for surveillance of minimal residual disease or disseminated retinoblastoma. While the standard of care remains morphological detection of disseminated cancer cells by cytology, studies in limited patients have shown that molecular detection might be more the more sensitive approach.[19,20] For UNI nonheritable (RB1-initiated) retinoblastoma cases, either of the tumor RB1 mutations can be used to detect disseminated cancer.[20] For heritable cases, the M2 (nonconstitutional) RB1 mutation can be used instead.[20] Furthermore, copy-number analysis of any of the post-RB1 loss genetic events that occur in the tumor,[19] or even MYCN for MYCN<sup>amp</sup> tumors, can be used as markers for molecular surveillance. Gene expression of GD2 synthase has also been studied as a molecular marker for disseminated retinoblastoma.[21] Further research remains to be done to support the routine implementation of molecular surveillance into practice.

**Retinoblastoma genetic counseling**

If complex genetic information is difficult for even the most seasoned of clinicians to understand, then the task of disseminating these findings to patient families becomes even more difficult. In some settings (mainly Europe and North America), genetic counselors may assist in educating patient families about retinoblastoma genetics. In many places around the world, however, this task is often left to the discretion of the treating physician. Recommendations for counseling in the presence and absence of retinoblastoma genetic testing are available,[18] however, it is becoming increasingly clear that the counseling approach may be influenced by context.[22-25] Further research is necessary to develop services that take into account the unique sociocultural context of the setting in question.[24] As advances genomic approaches lead the way forward to individualized medicine, it is important to study how well the medical community and public is equipped to understand the essential genetic concepts that facilitate informed consent, care, and follow-up. These approaches too will vary worldwide.

**Retinoblastoma genetics in India – scoping review**

**Study sample**

A search of PubMed for the keyword “retinoblastoma” with author affiliations in India yielded 270 citations [Supplementary File]. Excluding studies that were not exclusively focused on retinoblastoma (114), 156 remained. Of these, the 86 (55%) were clinical studies, 50 (32%) basic science, 14 (9%) clinical genetics, and 6 (4%) reviews [Fig. 2]. The Google search did not yield any additional clinical genetics publications that fit our criteria.

**Indian research on retinoblastoma genetics**

The 14 retinoblastoma clinical genetics studies came from four centers in India, covering a period of the publication from 2001 to 2011 [Table 1]. Full-text copies of only 13/14 publications could be located, thus 1 publication was excluded from the study [Table 1, Fig. 2].

The purpose of the studies ranged from reporting on the results of comprehensive molecular RB1 testing (6), evaluation of a specific methodology for RB1 testing (4), correlating molecular RB1 result to functional consequence on RB1 (2) and evaluating cost-effectiveness of molecular testing (1) [Table 1]. Many studies included commentary about the discovery of new RB1 mutations. No studies reported on the genetic counseling or general implementation of molecular genetic testing into clinical practice in India.

Only 4/6 studies reporting RB1 mutation discovery (representing 2 institutions) provided enough data such that the sensitivity of BI and UNI testing could be determined [Table 2]. Where data were provided, BI and UNI

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**Figure 2: Scoping review flow diagram.** A search of PubMed for the keyword “retinoblastoma” with author affiliations in India yielded 270 citations. Excluding studies that were not exclusively focused on retinoblastoma (114), 156 remained. Of these, the 86 (55%) were clinical studies, 50 (32%) basic science, 14 (9%) genetics, and 6 (4%) reviews. Full-text articles were located for 13/14 of the genetics publications, as illustrated.
| Number | Title                                                                 | Authors                                                                                           | Journal            | Year | Purpose                                           | Institute                  | Sensitivity |
|--------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------|------|---------------------------------------------------|----------------------------|-------------|
| 1      | Prediction of retinoblastoma and osteosarcoma: Linkage analysis of families by using polymorphic markers around RB1 locus | Chunder N, Basu D, Roy A, Roychoudhury S, Panda CK                                               | J BUON             | 2003 | Excluded; no full text available                 | Chitaramanj National Cancer Institute | NA          |
| 2      | Mutational analysis of the RB1 gene in Indian patients with retinoblastoma | Ata-ur-Rasheed M, Vemuganti GK, Honavar SG, Ahmed N, Hasnain SE, Kannabiran C                     | Ophthalmic Genet   | 2002 | Comprehensive RB1 mutation testing               | LV Prasad                  | Yes         |
| 3      | Mutational screening of the RB1 gene in Indian patients with retinoblastoma reveals eight novel and several recurrent mutations | Kiran VS, Kannabiran C, Chakravarthi K, Vemuganti GK, Honavar SG                                  | Hum Mutat          | 2003 | Comprehensive RB1 mutation testing               | LV Prasad                  | Yes         |
| 4      | A comprehensive, sensitive and economical approach for the detection of mutations in the RB1 gene in retinoblastoma | Parsam VL, Kannabiran C, Honavar S, Vemuganti GK, Ali MJ                                       | J Genet            | 2009 | Comprehensive RB1 mutation testing               | LV Prasad                  | Yes         |
| 5      | RB1 gene mutations in retinoblastoma and its clinical correlation    | Ali MJ, Parsam VL, Honavar SG, Kannabiran C, Vemuganti GK, Reddy VA                              | Saudi J Ophthalmol | 2010 | Functional consequence of RB1 mutation           | LV Prasad                  | NA          |
| 6      | Splicing aberrations caused by constitutional RB1 gene mutations in retinoblastoma | Parsam VL, Ali MJ, Honavar SG, Vemuganti GK, Kannabiran C                                       | J Biosci           | 2011 | Functional consequence of RB1 mutation           | LV Prasad                  | NA          |
| 7      | Genetic profile of 81 retinoblastoma patients from a referral hospital in southern India | Harini R, Ata-ur-Rasheed M, Shanmugam MP, Amali J, Das D, Kumaramanickavel G                     | Indian J Ophthalmol | 2001 | Evaluation of specific methodology (cytogenetics) | Sankara Nethralaya          | NA          |
| 8      | Molecular-genetic analysis of two cases with retinoblastoma: Benefits for disease management | Kumaramanickavel G, Joseph B, Narayana K, Natesh S, Mamatha G, Shanmugam MP, Elampanathi A, Biswas J | J Genet            | 2003 | Comprehensive RB1 mutation testing               | Sankara Nethralaya          | Incomplete  |
| 9      | Methylation status of RB1 promoter in Indian retinoblastoma patients | Joseph B, Mamatha G, Ramam G, Shanmugam MP, Kumaramanickavel G                                   | Cancer Biol Ther   | 2004 | Evaluation of specific methodology (methylation) | Sankara Nethralaya          | NA          |
| 10     | Retinoblastoma: Genetic testing versus conventional clinical screening in India | Joseph B, Shanmugam MP, Srinivasan MK, Kumaramanickavel G                                   | Mol Diagn          | 2004 | Cost-effectiveness of RB1 mutation testing       | Sankara Nethralaya          | NA          |
| 11     | Karyotyping in retinoblastoma-a statistical approach                 | Joseph B, Paul PG, Elampanthi A, Roy J, Vidhya A, Shanmugam MP, Kumaramanickavel G               | Asian Pac J Cancer Prev | 2005 | Evaluation of specific methodology (karyotype)   | Sankara Nethralaya          | NA          |

Contd...
sensitivity ranged in reports from the same institutions, an overall sensitivity of combined cases from that one center was calculated. BI sensitivity ranged from 36% to 75%, and UNI sensitivity ranged from 26% to 35% [Table 2]. Table 2 provides more details on number of specimens tested by each laboratory in their respective reports.

**Way forward**

The main purpose of this article was to review the current knowledge of retinoblastoma genetics as it relates to patient care, and juxtapose that alongside published evidence of retinoblastoma genetic testing as it is implemented in India.

Is genetic testing part of the standard of care for retinoblastoma in India? While certainly there exist laboratories that provide retinoblastoma genetic testing, this review did not consider possible barriers (social, economic, etc.) that may prevent a family from benefiting from the service. That some families may access retinoblastoma testing from international laboratories was also not considered. The review also did not consider institutional or logistical limitations that may prevent a laboratory from achieving reliable, high-quality results, nor were nonacademic publications from commercial labs that might offer retinoblastoma genetic testing surveyed. However, this review of academic research on retinoblastoma genetics within the Indian context does suggest the existence of a “know-do” gap: The current knowledge of retinoblastoma genetics does not appear to be implemented comprehensively in India. While a handful of laboratories in India have published their experience with RB1 genetic testing, the quality of reports varies, and it is difficult to ascertain how reliable testing is from different institutions [Table 2]. For the practicing physician caring for retinoblastoma children, reliability of results is imperative, as it affects their choice of subsequent treatment and surveillance plan.

One major concern that emerged from looking at reports of molecular testing for retinoblastoma is that test sensitivity is not consistently reported. Often an overall sensitivity for BI and UNI cases was reported, and the sensitivity reported in this paper had to be calculated with the raw data – and in some cases, this raw data was not reported. Test sensitivity is important information that every retinoblastoma practitioner must arm themselves with in order to practically interpret the results of a given report.

A low test sensitivity does not necessarily mean that a given laboratory should be avoided; rather, an honest account of the sensitivity allows for an educated decision after a “no mutation found” result if it is used to conduct genetic testing. For example, one of the centers in this review had a sensitivity of 83% for BI cases in their more recent publication [Table 2]. A physician receiving a “no mutation found” result from this laboratory may wish to have the specimen re-tested by a lab with a higher sensitivity. There are many innovative approaches to be explored, not just for laboratories to improve their own sensitivity, but for physicians who order these tests to maximize use of available resources and get the results they need for their patients.

While sensitivity appears to be ignored or inadequately calculated in some reports, despite its clinical importance, it is striking to see how often novel RB1 mutations are reported in the literature. It is well known that the RB1 gene can be
Table 2: RB1 mutation detection sensitivity

| Number | Institution     | Number of patients | Number of BI patients | Number of BI blood studied | Number of M1 found | BI sensitivity (%) | Number of UNI patients | Number of UNI tumors studied | Number of UNI M1/ M2 found | UNI sensitivity (%) |
|--------|-----------------|--------------------|-----------------------|----------------------------|--------------------|--------------------|------------------------|-----------------------------|--------------------------|----------------------|
| 2      | LV Prasad       | 21                 | 12                    | 12                         | 5                  | 42                 | 9                      | 2                           | 2                        | 100                  |
| 3      | LV Prasad       | 47                 | 32                    | 20                         | 15                 | 75                 | 15                     | 15                          | 4                        | 27                   |
| 4      | LV Prasad       | 74                 | 53                    | 53                         | 44                 | 83                 | 21                     | 0                           | NA                       | NA                   |
| 14     | TATA Memorial   | 34                 | 11                    | 11                         | 4                  | 36                 | 23                     | 23                          | 6                        | 26                   |

BI: Bilateral, UNI: Unilateral, M1: First RB1 mutation, M2: Second RB1 mutation, NA: Not available

Damaged in any number of ways – new types of mutations are the norm for retinoblastoma, and rarely result in novel clinical significance to the patient. Perhaps it is time to re-examine the focus of retinoblastoma genetics research. For example, increasing a laboratory’s capability to find all existing RB1 mutations (i.e. improving sensitivity) through novel approaches is a significant finding; finding a new way that the RB1 gene can be potentially damaged (while failing to detect the majority of RB1 mutations in other patients), is not.

Much like the rest of the world, the Indian research focus for retinoblastoma centers around clinical and basic science, with little focus on clinical genetics or its implementation into practice [Fig. 2, Supplementary File]. However, India is in the unique position of carrying the highest burden of retinoblastoma in the world.[27] There is much more to be gleaned in this context to bridge the retinoblastoma genetics “know-do” gap. This new information and knowledge, once generated, could have vast utility for the global retinoblastoma population. There is no shortage of Indian intellect and people-power to produce groundbreaking research and new knowledge. Particularly, in this current era of genomic advances, there is much to be done for the benefit of Indian children with retinoblastoma, and by default the rest of the world. Still, the literature does not seem to indicate this power is being harnessed just yet. With a careful, evidence-based approach, India can rise to its potential and be a leader in the next wave of genetic research and care for retinoblastoma.

Supplementary File: Detailed list of all 270 citations resulting from PubMed Search.

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Cite this article as: Dimaras H. Retinoblastoma genetics in India: From research to implementation. Indian J Ophthalmol 2015;63:219-26.

Source of Support: Nil. Conflict of Interest: None declared.