Malignancy in Neurofibromatosis Type 1

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ABSTRACT

Neurofibromatosis type 1 (NF1) represents a major risk factor for development of malignancy, particularly malignant peripheral nerve sheath tumors (MPNST), optic gliomas, other gliomas, and leukemias. The oncologist will see NF1 patients referred for treatment of malignancy, and should be alert to the possibility of undiagnosed NF1 among patients with cancer. Brain tumors tend to have a more indolent course in NF1 than in the general population, and hence are best managed conservatively. MPNST, in contrast, do not respond to standard chemotherapy or radiation therapy. The most effective treatment of MPNST appears to be early diagnosis and surgery, but early diagnosis is hampered by frequent occurrence within preexisting large tumors, making new growth or change difficult to detect. New insights into pathogenesis now offer hope of development of specific methods of treatment with reduced toxicity and more precise molecular targeting. There is an urgent need, however, to develop methods to measure tumor growth and monitor outcomes, develop preclinical drug screening systems, and further explore the pathogenesis of the disorder to determine whether mechanisms other than Ras regulation may be important in pathogenesis. The Oncologist 2000;5:477-485

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder, the cardinal feature of which is the development of multiple peripheral nerve sheath tumors called neurofibromas. Other characteristics include pigmentary changes in the skin, skeletal anomalies, and learning disabilities. Although neurofibromas are benign tumors, malignant peripheral nerve sheath tumors (MPNST) may occur. In addition, gliomas, particularly pilocytic astrocytomas of the optic nerve, and leukemias, are seen with increased frequency in the NF1 population. The gene responsible for NF1 has been cloned [1-4], and encodes a protein referred to as “neurofibromin.” Although the function of neurofibromin is not completely understood, it is known to include a GTPase activating protein (GAP) domain that regulates hydrolysis of Ras-GTP to Ras-GDP [5-8]. This emerging understanding of the pathophysiology of NF1 has suggested new avenues of treatment involving the use of Ras inhibitors.

Although only a minority of patients with NF1 develops malignancy as a complication of their disorder, cancer remains an important cause of morbidity and mortality in the disorder. Moreover, oncologists may encounter patients with NF1 in the course of treatment for cancer, and need to be familiar with the diagnosis of the disorder and its clinical features. This review will focus on the malignant complications of NF1, but will also provide an overview of the condition and consider possible new avenues for treatment.

OVERVIEW OF THE NF1 PHENOTYPE

NF1 is one of two disorders referred to collectively as the “neurofibromatoses,” the other being NF2 [9]. Nerve sheath tumors are also characteristic of NF2, but in NF2 the lesions are schwannomas, not neurofibromas. The cardinal manifestations of NF1 and NF2 are summarized in Table 1. Although the tumors of NF2 can cause substantial morbidity and even be life-threatening, they rarely display a malignant histology. Therefore, this review will focus on NF1.

NF1 is diagnosed on the basis of clinical criteria (Table 2) [9, 10]. Although the gene has been cloned, the wide diversity of pathogenic mutations and large size of the gene have impeded the development of a clinical diagnostic test [11, 12]. Fulfillment of two or more diagnostic criteria is required for a definitive diagnosis of NF1. Since many of the criteria are age-dependent,
it is often necessary to follow a child with suspected NF1 for several years before the diagnosis can be confirmed. The disorder should be suspected in any child or adult that presents with a neural sheath tumor or central nervous system glioma in the presence of multiple café-au-lait spots and/or a family history of neural or CNS malignancy. Diagnostic evaluation consists of a skin examination for café-au-lait macules, skin-fold freckles, and neurofibromas; a slit lamp examination looking for iris Lisch nodules; and a thorough physical and neurological examination. Imaging studies such as brain magnetic resonance imaging (MRI) are not generally done solely to establish a diagnosis. Children with NF1 may have optic glioma or areas of enhanced T2 signal intensity, but the clinical impact of finding these lesions, and the diagnostic specificity of the enhanced T2 spots, may not justify the expense, anxiety, and sedation risk of performing MRI in young children [13].

Table 3 lists the major complications of NF1 by system. The overall degree of severity and specific complications in

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<thead>
<tr>
<th>Feature</th>
<th>NF1</th>
<th>NF2</th>
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<tr>
<td>Frequency</td>
<td>1:3,500</td>
<td>1:40,000</td>
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<tr>
<td>Inheritance</td>
<td>Autosomal dominant</td>
<td>Autosomal dominant</td>
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<tr>
<td></td>
<td>50% new mutation</td>
<td>50% new mutation</td>
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<tr>
<td>Tumor types</td>
<td>Neurofibroma</td>
<td>Schwannoma</td>
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<tr>
<td></td>
<td>Glioma</td>
<td>(especially vestibular)</td>
</tr>
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<td></td>
<td>Malignant peripheral nerve sheath tumor</td>
<td>Ependymoma</td>
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<td></td>
<td>Nonlymphocytic leukemia</td>
<td>Meningioma</td>
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<td></td>
<td>Pheochromocytoma</td>
<td>Gioma</td>
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<td>Nontumor manifestations</td>
<td>Learning disability</td>
<td>Posterior subcapsular</td>
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<tr>
<td></td>
<td>Skeletal dysplasia</td>
<td>cataract/cortical wedge</td>
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<td></td>
<td>Vascular stenosis</td>
<td>opacity</td>
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<tr>
<td></td>
<td>Café-au-lait macules</td>
<td></td>
</tr>
<tr>
<td>Gene locus</td>
<td>Chromosome 17</td>
<td>Chromosome 22</td>
</tr>
<tr>
<td>Gene</td>
<td>Neurofibromin</td>
<td>Merlin (schwannomin)</td>
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<td>GAP protein</td>
<td>Cytoskeletal protein</td>
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Table 2. Diagnostic criteria for NF1

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<tr>
<th>Diagnostic Criterion</th>
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<tr>
<td>Café-au-lait macules (6 or more larger than 5 mm before puberty or 15 mm after puberty)</td>
<td>Usually appear in early months of life and are visible by 2 years of age; 10% of people in general population have 1 café-au-lait macule.</td>
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<td>Skin-fold freckles (axillae, groins, neck, under breasts)</td>
<td>Usually appear between 3-5 years old, highly specific to NF1.</td>
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<td>2 or more neurofibromas or 1 plexiform neurofibroma</td>
<td>Plexiform neurofibroma is neurofibroma involving multiple fascicles of a nerve and its branches, and may be associated with soft tissue hypertrophy.</td>
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<tr>
<td>2 or more iris Lisch nodules</td>
<td>Requires use of slit lamp to distinguish from iris nevi; highly specific to NF1.</td>
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<td>Optic glioma</td>
<td>15% of children with NF1 have optic nerve thickening by MRI. Generally clinically visible in first year of life in those who will develop this.</td>
</tr>
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<td>Characteristic skeletal dysplasia (tibial dysplasia, orbital dysplasia)</td>
<td>Severity may vary widely among members of the same family.</td>
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<tr>
<td>Affected first-degree relative</td>
<td></td>
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an individual are unpredictable. It is estimated that two-thirds of individuals with NF1 are relatively mildly affected, not requiring major surgery or having life-threatening problems [14]. Genotype-phenotype correlations have not been established, with one exception: individuals with complete deletion of the NF1 gene tend to have dysmorphic features, severe developmental delay, and early onset of a large number of neurofibromas [15, 16].

**Frequency of Cancer in NF1**

Estimation of the frequency of malignancy in NF1 is made difficult by bias of ascertainment and admixture of malignancies that might occur in affected individuals but which are not related to NF1 [17]. Blatt et al. [18] reviewed the types of malignant tumors seen in 121 children with neurofibromatosis. Sarcomas were seen in three; 17 had brain tumors, including nine optic gliomas and three malignant astrocytomas; two had acute myelogenous leukemia. The presence of two children with bilateral vestibular schwannomas indicates admixture of NF2 in this study population. The study also was likely to have been biased by ascertainment at a major pediatric cancer center. A population-based study done by Huson et al. [19] provides the data set least likely to be biased towards ascertainment of cancer. The frequency of glioma (excluding optic glioma) was 1.5% and of non-central nervous system (CNS) malignancy (mainly sarcomas) 2.9%, for a combined frequency of 4.4%. Using an international NF1 database, Friedman and Birch [20] reported a frequency of CNS neoplasms (excluding optic gliomas) of 2.0% in probands and 1.2% in NF1-affected relatives, and of non-CNS neoplasms (excluding neurofibromas) of 4.9% in probands and 3.2% in affected relatives. Sørensen et al. [21] reported a long-term follow-up of 212 Danish patients with NF1. The relative risk of malignancy in this population was 4.0 (95% confidence limits 2.8-5.6).

Another approach to study the risk of cancer in NF1 is to search for NF1 cases among a large population of cancer patients. Matsui et al. [22] reviewed data from 26,084 Japanese children with cancer and found 56 with NF1, 6.45 times the expected number. Tumor types in the NF1-affected children included optic glioma, other CNS glioma, MPNST, rhabdomyosarcoma, and leukemia. Baptiste et al. [23] found a dramatically increased relative risk of brain tumor in individuals with NF1 in a New York population-based case-control study of CNS tumors.

**MPNST**

The MPNST, in the past also referred to as “malignant schwannoma” or “neurofibromosarcoma,” can occur in the general population but is one of the hallmark complications of NF1. D’Agostino et al. [24] reported a clinical study of MPNST in 1963, and Ducatman et al. [25] updated this study in 1986. Of 120 MPNST included in the latter paper, 62 (52%) were from patients with NF1. Mean age at diagnosis for NF1 patients was younger (28.7 years) than for non-NF1 patients (34.0 years); the age range for those with NF1 was 7-62 years. Presenting signs were most commonly pain, enlarging tumor mass, or neurological deficit due to nerve compression. Pathological examination revealed a coexisting benign neurofibroma in 81%, suggestive of origin from a preexisting tumor.

Outcome of treatment of MPNST remains poor. In the Ducatman et al. study, five-year survival of NF1 patients with MPNST was 16%, compared with 53% for non-NF1 patients. Metastases occurred in 39% of NF1 patients, most commonly to lung, and also to soft tissue, bone, liver, abdominal cavity, adrenal glands, diaphragm, mediastinum, brain, ovaries, kidneys, and retroperitoneum. Prognosis correlated with tumor size and extent of resection, but not with radiation or chemotherapy. Wanebo et al. [26] reviewed 28 patients with MPNST, including 15 with NF1. They did not find a difference in survival in the NF1 versus non-NF1 groups, but confirmed that survival was influenced by surgery, but not radiation or chemotherapy. Similar results were reported for children with MPNST by Raney et al. [27], in a survey that included 11 NF1 patients with PNST by Doorn et al. [28] and Shearer et al. [29].

Clinicians should be alert to unexpected growth of a preexisting neurofibroma, particularly a plexiform neurofibroma, or the occurrence of unexplained pain. It is clear that most, if not all, MPNST in NF1 patients arise from preexisting neurofibromas. Diagnosis of malignancy is complicated by the fact that benign neurofibromas often grow, and may be painful, particularly in response to trauma. Also, a malignant component may represent a small portion of a large plexiform tumor, and may be missed if a biopsy is performed. MRI does not reliably distinguish malignant from nonmalignant tissue within a neurofibroma. Gallium scanning has been reported as being useful in the detection of MPNST in one study [30], but the utility of this approach has not been confirmed. Ferner et al. [31] have used (18)fluorodeoxyglucose positron emission tomography to detect MPNST. Increased uptake was found to be characteristic of MPNST, but there was overlap between some benign plexiform neurofibromas and MPNST.

Mutation of both copies of the \textit{NF1} gene has been demonstrated in MPNST [32], but this appears to be characteristic of benign neurofibromas as well [33], and therefore cannot be sufficient for malignant change. It is likely that additional genetic changes, such as loss of function of \textit{p53}, contribute (see below). DeClue et al. [34] have demonstrated epidermal growth factor receptor (EGF-R) expression and function in MPNST, including both primary tumors and cell lines. EGF-R expression is not characteristic of normal
Schwann cells, suggesting that activation of EGF-R may be involved in the process of malignant change.

**OPTIC GliOMA**

Optic glioma is the most common CNS tumor seen in association with NF1, and has been the subject of the most controversy regarding diagnosis and treatment. Optic glioma is mainly a tumor of childhood. A survey of individuals with NF1 by computerized tomography scanning revealed signs of optic glioma in 15% [35]. Tumors involved the optic nerve, chiasm, or both, and were either unilateral or bilateral. Two-thirds were unsuspected clinically. **Listernick et al.** [36] employed MRI screening in 176 children with NF1 and identified optic gliomas in 33 (19%). Only eight had symptoms such as proptosis or precocious puberty at the time of diagnosis and 64% had normal ophthalmological examinations. Abnormal ophthalmological findings included loss of visual acuity, proptosis, abnormal color vision, optic atrophy, and afferent pupillary defect. Precocious puberty in NF1 is usually a sign of chiasmatic optic glioma with hypothalamic involvement [37, 38].

Although optic glioma is common in children with NF1, its natural history is often indolent, raising questions about the ideal approach to diagnosis and treatment. **Hoyt and Baghdassarian** [39] originally recognized the potential for optic gliomas to pursue a benign course. **Listernick et al.** [36] found no evidence for tumor progression in 23/26 children with NF1 and optic glioma who were followed for a median period of 2.4 years (range 0.2-7.2 years). Similarly, **Kuenzle et al.** [40] reported that in 10/13 children with NF1 and optic glioma whose tumors were not treated, the tumors remained stable in size over a period of follow-up ranging from 2-18.5 years. An indolent course for optic glioma was also noted in a retrospective study by **Pascual-Castroviejo et al.** [41]. Early diagnosis of optic glioma is possible using MRI screening, although there are well-documented instances in which an initial MRI was negative for optic glioma, yet a tumor appeared on a repeat study done years later [42]. This raises the question of the value of an initial screening study. Spontaneous regression of optic glioma without treatment has also been reported [43]. Visual evoked potentials can detect early signs [44], but the sensitivity of this test has been challenged [45]. The utility of these approaches to early diagnosis is questionable given that treatment is reserved for instances of symptomatic progression. A review by the National Neurofibromatosis Foundation Taskforce on Natural History of Optic Glioma recommended annual ophthalmological examination, reserving special studies for follow-up of abnormal clinical findings [46].

Nevertheless, it is clear that a subset of optic gliomas in children with NF1 do require treatment [47-49]. Surgery is rarely done; biopsy is unnecessary for optic nerve or chiasm expansions in children with NF1, and surgery is reserved for instances of complete visual loss, severe proptosis, or rare instances of associated hydrocephalus. In the past, radiation therapy was the most commonly used treatment, with good results in terms of tumor control [50], but frequent neuropsychiatric, endocrine, and vascular complications [51, 52]. More recent results with carboplatin [53] or vincristine/carboplatin have shown encouraging results [54].

**Other Glioma**

Aside from optic glioma, gliomas can occur throughout the neuraxis in individuals with NF1. **Ilgren et al.** [55] reviewed the neuropathology of 89 gliomas in 87 NF1 patients. Forty-three were optic gliomas; the remainder were cerebellar astrocytomas (15) or ependymomas (2), third-ventricle astrocytomas (11), cerebral astrocytomas (11), brain stem gliomas (4), and spinal cord tumors (3). The frequency of malignant change in these tumors was found to be higher than in tumors at comparable sites in the non-NF1 population.

Brain stem tumors in children with NF1 have posed a particularly vexing problem. Although gliomas at this site in the general population are typically associated with poor prognosis, those that occur in individuals with NF1 may have a more indolent course and often do not require treatment [56]. **Pollack et al.** [57] found that only 9/21 brain stem gliomas in their NF1 cohort were symptomatic and only four required treatment. Seven of ten patients whose tumors progressed radiographically subsequently stabilized or spontaneously regressed. A higher proportion, 15/17, of tumors studied by **Molloy et al.** [58] were associated with neurological symptoms, but all 15 had survived after a median follow-up of 52 months, again indicative of a less malignant course of NF1-associated brain stem tumors compared with similar tumors in the general population. Conservative management, withholding treatment except for individuals with radiographic progression associated with neurological signs or symptoms, seems appropriate for brain stem tumors, as for optic gliomas, in association with NF1.

**Leukemia**

**Bader et al.** [59] reported an increased proportion of non-lymphocytic leukemia among children with NF1 and leukemia. **Stiller et al.** [60] conducted a population-based study and found an increased relative risk of chronic myelomonocytic leukemia, acute lymphoblastic leukemia, and non-Hodgkin’s lymphoma in the NF1 population. Juvenile xanthogranuloma (JXG), cutaneous nodules consisting of histiocytes, is found with increased frequency in children with NF1 and also has been correlated with risk of juvenile chronic myelogenous leukemia (JCML) in the general population. Although it has been suggested that individuals with NF1 and JXG are at increased risk of JCML [61], this association has not been
conclusively demonstrated, and it is not clear that there is clinical benefit to close observation of children with NF1 and JXG.

Leukemic cells from NF1 patients have loss of heterozygosity for the NF1 gene [62], but do not have activating Ras mutations, in contrast with many non-NF1-associated myeloid malignancies [63]. Increased levels of Ras-GTP are found in the NF1-associated leukemias [64] and the leukemic cells show hypersensitivity to GM-CSF [65] and other cytokines [66].

**Other Malignancy**

Many other benign and malignant tumors have been proposed as being associated with NF1. Rhabdomyosarcoma [22] and pheochromocytoma [67] are seen with disproportionately high frequency in individuals with NF1. For other tumors, however, the data are less clear, either because the tumors are rare even in those with NF1, or because the tumors are also common in the general population. Stay and Vawter [68] reported three instances of NF1 among 342 cases of Wilms’ tumors, but the association of NF1 and Wilms’ tumor has not been confirmed in subsequent studies. Similarly, reported associations of neuroblastoma and NF1 may be accounted for by chance [69].

**Molecular Pathogenesis and Insights into Treatment**

Schneider et al. [70] reviewed histories of 45 children with NF1 and malignancy, and could not identify risk factors related to other clinical features of NF1, although they did notice a tendency towards familial aggregation of malignant tumors in familial cases of NF1. This raises the possibility that there may be NF1 mutations that increase the risk of malignancy, although no such mutation has been identified so far. It is also possible that mutations in other genes that predispose to malignancy in the general population might increase the risk of NF1-associated malignancy when present in individuals with neurofibromatosis.

There is a substantial body of evidence that supports the hypothesis that NF1 functions as a tumor suppressor in the pathogenesis of at least some of the tumors seen in the disorder. This includes finding loss of heterozygosity or homozygous mutation of the NF1 gene in benign neurofibromas [33], as well as many malignant tumors (summarized above). In addition, mice rendered heterozygous for an NF1 mutation develop leukemias and sarcomas [71], and mice that are chimeric for cells with homozygous NF1 mutation develop neurofibroma-like tumors [72]. Loss of neurofibromin function is probably a critical event in the formation of neurofibromas, but, at least in neural tissues, is not sufficient to result in malignancy. There is evidence to support a role of p53 in the formation of MPNST. Mice that are heterozygous for both an NF1 and p53 mutation develop sarcomas [72, 73], and human MPNST have been found to have mutation of p53 in addition to NF1 [74]. It is possible that other dominant or recessive oncogenes also contribute towards malignancy in other NF1-associated lesions.

The NF1 gene product, neurofibromin, is a 2818 amino acid protein that contains a functional GAP domain that acts on Ras-GTP [5-7]. Elevated levels of Ras-GTP have indeed been found in some malignancies from patients with NF1 [64, 75], supporting the hypothesis that regulation of Ras is a critical function of neurofibromin. The GAP-related domain of neurofibromin, however, represents only a portion of the entire protein; the function of the remainder of the molecule is unknown, although recent mutation analysis has pointed towards another region upstream of the GAP-related domain involving exons 11-16 that is a target for missense mutation, and hence may be an important functional domain [12].

The apparent role of Ras in the pathogenesis of tumors in NF1 has made it an attractive target for new approaches to therapy [76]. Among the most promising new agents are inhibitors of farnesyl protein transferase enzymes that are required for attachment of Ras to the cell membrane [77, 78]. Phase I trials indicate that these drugs are well tolerated [79, 80], although preclinical tests with one drug in NF1 mouse knockout leukemia model did not demonstrate therapeutic benefit [81]. It is likely that phase II trials in NF1 patients, including those with debilitating plexiform neurofibromas or malignant tumors, will begin in the near future. Other Ras inhibitors, such as antisense RNA [82, 83], may also have a role in clinical trials, as may inhibitors of angiogenesis.

Clinical trials in patients with NF1 present several challenges that are different from other trials of antineoplastic agents. Many of the benign tumors in NF1, especially plexiform neurofibromas, tend to be large and irregular, and hence are difficult to measure to follow growth or regression. Also, growth rates of both benign and malignant lesions can be unpredictable, with long periods of stasis or even spontaneous regression. Finally, malignant tumors in NF1 patients are likely to have more complex genetic changes than benign tumors; failure of a drug in treatment of a malignant lesion therefore does not necessarily predict failure in treatment of benign, but debilitating, plexiform neurofibromas. These challenges will require careful attention to therapeutic endpoints, recognizing that NF1 is a chronic disorder and that the slow-growing tumors may not respond to cytotoxic agents. There is currently a multicenter study of the natural history of plexiform neurofibromas that is developing a body of normative data on plexiform neurofibroma growth and testing the ability of volumetric MRI to detect changes in the rate of tumor growth (Fig. 1). There is also a need for development of preclinical testing systems.
for new drugs. The relatively small number of NF1 patients with malignancy will make it difficult to accumulate large cohorts for clinical trials. It will therefore be particularly important to have a system of preclinical screening to identify drugs that are most likely to be effective and worthy of testing in patients.

**CONCLUSION**

Malignancy is an important component of the NF1 phenotype, and one of the few life-threatening complications. The frequency of malignancy is often overstated, however, largely due to biased reporting of patients with the most severe manifestations. Furthermore, the natural history of malignancy in patients with NF1 is often different from that of similar tumor types in the general population. CNS tumors, in particular, tend to be less aggressive in NF1 patients. The diagnosis of NF1 is therefore relevant to the process of deciding whether to initiate treatment of a CNS neoplasm. The NF1 gene was cloned ten years ago, and, although it is clear that the Ras protein is involved in the pathogenesis of tumors, this is just now leading to the first trials of molecularly targeted therapies. Much remains to be learned about the pathogenesis of NF1, however, in addition we need new resources for preclinical drug testing and clinical outcomes measurement in order to translate this new knowledge to useful clinical application.

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