Interventions to Improve Treatment of Osteoporosis Following Fracture

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Abstract

• **Objective:** To review the approach to osteoporosis treatment following fracture.
• **Methods:** Review of the literature.
• **Results:** Despite the tremendous medical and economic impact of osteoporotic fractures, the majority of older patients with fragility fractures do not subsequently receive appropriate evaluation and therapy for osteoporosis. Relatively simple interventions can increase the likelihood that a patient who sustains a fracture will receive subsequent evaluation and therapy; however, the implementation of interdisciplinary approaches and coordination of fracture treatment among primary care providers, orthopedists, metabolic bone experts, dietitians, physical therapists, and other pertinent health care professionals has been a challenge for health care delivery systems. The comprehensive management of osteoporosis includes evaluation of bone mineral density, assessment for secondary causes of low bone density, initiation of nonpharmacologic therapies such as improved nutrition and physical activity, and selection of appropriate pharmacologic therapy. Effective pharmacologic options now include oral or intravenous bisphosphonates, anabolic therapy with parathyroid hormone, selective estrogen receptor modulator therapy with raloxifene, intranasal calcitonin, and estrogen therapy.
• **Conclusion:** Individual clinicians and health systems alike must minimize missed opportunities for meaningful secondary prevention of fractures, especially as the options expand for safe and efficacious treatment of osteoporosis.

A pproximately 1 in 2 white women and 1 in 5 men will experience an osteoporosis-related fracture in their lifetimes [1]. The medical impact of these fractures is tremendous: mortality after hip fracture approaches 25% at 1 year [2], and of those who survive the postfracture period, only half recover their prefracture functional status with respect to activities of daily living [3]. Economically, the direct cost of the 1.5 million osteoporotic fractures in the United States each year is estimated at $18 billion [4]. Until a fracture occurs, osteoporosis is a silent disorder, and the assessment of fracture risk in an asymptomatic patient continues to evolve. For the patient who has already experienced a fracture, however, the decision making is somewhat less complex: a history of fragility fracture (resulting from a fall from standing height or less, or unrelated to substantial trauma) in a postmenopausal woman or an older man strongly indicates skeletal fragility and predicts an increased risk of future fracture [5]. The presence of a vertebral fracture, even if asymptomatic, increases the risk of future vertebral fracture fivefold and doubles the risk of hip fracture [6]. Even fractures that appear traumatic also predict increased future fracture risk [7]. Unfortunately, the majority of older patients who have fractured do not subsequently receive appropriate therapy for osteoporosis, even if the fracture required hospitalization [8]. This gap in osteoporosis care has been well documented: a retrospective study of 300 women aged 50 years and older with a history of fracture, for example, found that more than 50% were not receiving any treatment for osteoporosis [9]. Another study of 3492 postmenopausal women with a history of spine, hip, or wrist fracture found that the older a patient was, the less likely the patient was to receive pharmacologic therapy for osteoporosis [10]. It would be preferable to capture high-risk patients prior to fracture, but it is clear that even the unequivocal signal of skeletal fragility, a low-trauma fracture, is not resulting in appropriate intervention [11].

Strategies to Encourage Intervention Following Fracture

While ample observational data exist regarding osteoporosis management after fracture [12], there are few randomized trials of interventions to improve management specifically in fracture patients [13–17]. In 1 recent trial, patients who had suffered radial fractures were randomized such that the orthopedic surgeon either ordered bone mineral density

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(BMD) testing with results faxed to patients’ primary care providers or sent letters to the primary care providers outlining guidelines for osteoporosis screening. Ninety-three percent of those in the first group, compared with 30% in the second group, underwent BMD testing, and 75% compared with 26% were prescribed therapy within 6 months of the fracture [13]. Another trial focused on women enrolled in a Pacific Northwest health maintenance organization who had suffered a fracture but had not yet undergone BMD measurement or initiation of medical therapy; when patient-specific postfracture advice was delivered to patients’ primary care providers, there was a significant increase in testing and in medication initiation compared with women assigned to usual care, although only half of patients in the intervention group received BMD measurement, medication, or both [14]. This trend—a significant improvement in osteoporosis management but with a persistent gap in care—was also identified by an investigation of patients enrolled in one of the largest integrated health delivery systems in Canada [15].

Other interventional studies have involved the assessment of osteoporosis care before and after the implementation of new programs. Some of these studies have found that the implemented intervention increased appropriate evaluation of patients but not appropriate treatment. For example, in a study at 5 large fracture clinics in Toronto, patients who received education from their orthopedic surgeons and letters addressed to their primary care physicians were more likely to undergo BMD testing than those in a similar cohort prior to the initiation of the intervention, but they were not more likely to receive treatment. However, BMD testing and treatment were assessed 3 months following the intervention, perhaps too short an interval to fully capture response to the intervention [18]. Of those pre- and postintervention studies that showcased successful approaches, many have been within well-structured health maintenance organizations or in countries with national health programs, such as a study of a comprehensive Fracture Liaison Program in Glasgow, Scotland, hospitals comprising 2 National Health Service trusts [19].

Since one of the barriers to evaluation and treatment of osteoporosis following fracture is the lack of clarity regarding the roles of orthopedic surgeons and primary care physicians in providing appropriate care, it is noteworthy that many interventions described in the literature are interdisciplinary, involving both groups of physicians and sometimes trained nurses providing specialized education or liaison services. Further, orthopedic organizations are participating in efforts to improve care. For example, the American Orthopaedic Association recently completed a pilot study and now has launched a larger “Own the Bone” initiative to identify patients who have had a fracture, to provide screening, education, and treatment, and to follow patients to assess for appropriate osteoporosis management [20,21].

Treatment of Osteoporosis Following Fracture
The comprehensive management of a patient with a fracture should address not only the acute fracture issues and subsequent rehabilitation but also the assessment of BMD, evaluation for secondary causes of bone loss, initiation of nonpharmacologic therapies, and selection of appropriate pharmacologic therapy.

Evaluation for Secondary Causes of Osteoporosis
The disorders that can contribute to bone loss are myriad, ranging from the common and easily diagnosed such as hyperparathyroidism to the rare and difficult to detect such as mastocytosis [22]. Other common conditions include nutritional disorders such as vitamin D and calcium deficiency; gastrointestinal disease that predisposes to intestinal malabsorption of vitamin D and calcium; endocrine disorders such as thyrotoxicosis; drugs such as glucocorticoids, anticonvulsants, and heparin; and other disease processes including renal disease, hypercalcemia, multiple myeloma, liver disease, and rheumatoid arthritis. In men, hypogonadism is a potential secondary cause. Evidence of these conditions should be sought from the medical history, physical examination, and pertinent laboratory tests.

There are conflicting assertions about which laboratory tests should be ordered routinely in a patient with osteoporosis. Data on this topic are largely limited to case series or patient cohorts derived from specialty clinics. One of the most systematically studied of such specialty clinic cohorts was that of 664 postmenopausal women with osteoporosis [23]. Women were excluded if they had histories of disease or medication known to affect bone adversely, leaving 173 women with no known contributor to osteoporosis; these women underwent a thorough laboratory evaluation. The authors found that 32% had a previously undiagnosed metabolic bone disorder. Based on the prevalence of disorders detected, they recommended routine evaluation of serum calcium, parathyroid hormone (PTH), 25-hydroxyvitamin D, and 24-hour urinary calcium levels, as well as thyroid-stimulating hormone level in women on thyroid hormone replacement. In contrast, a secondary analysis of a cohort of 15,316 postmenopausal women concluded that a low thyroid-stimulating hormone was the only abnormal laboratory test more common in women with low BMD or fracture than in women of normal BMD without fracture; of note, this study did not test 25-hydroxyvitamin D levels [24]. Studies have estimated that the prevalence of a secondary contributor to bone loss among osteoporotic patients is between 30% and 70% [25–28], and a recent study of patients with a history of hip fracture found that 80% had at least 1 previously undiagnosed condition [29]. Importantly, multiple abnormalities have been shown to coexist, so the presence of 1 known secondary cause of osteoporosis should not prohibit consideration of other causes.
There are several expert opinion-based guidelines on laboratory testing in patients with osteoporosis that provide overlapping, although varied, recommendations [22,30–33]. At the current time, every fracture patient should have a targeted history and physical examination as well as a routine chemistry panel and complete blood count. There should be a low threshold for testing thyroid function in all patients and gonadal function in men. The measurement of PTH, 25-hydroxyvitamin D, and urinary calcium should be considered strongly in fracture patients; older patients, particularly those with ongoing bone loss, should be evaluated for multiple myeloma. Other laboratory evaluation should be guided by the thorough history and physical examination.

**Nonpharmacologic Therapy**

Combined calcium and vitamin D supplementation has been shown to reduce fracture risk by 30% to 40% [34,35], but determining the individual effects of calcium and vitamin D has not been straightforward. A meta-analysis of 15 calcium intervention trials involving postmenopausal women found an increase of nearly 2% in spine BMD after 2 years in those taking calcium, although vertebral and nonvertebral fractures were not statistically decreased [36]. However, a recent randomized trial of 1200 mg/day of elemental calcium in patients with colorectal adenomas demonstrated a significant reduction in fracture over 4 years [37]. As calcium is a threshold nutrient, benefit may be limited to those individuals with marginal intakes at baseline. Several interventional trials and a meta-analysis have shown reductions in hip and nonvertebral fractures with vitamin D supplementation; a dose of 700 to 800 IU/day appears necessary to have this effect [38].

A total calcium intake of 1200 to 1500 mg/day (through diet, supplements, or both) is recommended for all postmenopausal women by the U.S. Surgeon General and by the National Osteoporosis Foundation (NOF) [1,39]; the NOF also makes that recommendation for men aged 50 years and older. Intakes in excess of 1500 mg/day do not appear to provide additional benefit and may increase the risk of kidney stones. The Food and Nutrition Board of the Institute of Medicine has set the adequate intake for vitamin D at 200 IU/day up to age 50 years, 400 IU/day for ages 51 to 70 years, and 600 IU/day for ages 71 and older [40]. However, most skeletal experts believe these recommended intakes should be increased, including the NOF, which recommends 800 to 1000 IU/day for adults aged 50 years and older. If measured, the goal for serum 25-hydroxyvitamin D values is greater than 30 ng/mL.

Nonpharmacologic recommendations also include weight-bearing and muscle strengthening exercise. In interventional trials, various exercise regimens with weight-bearing components have been shown to increase BMD [41–43]. Targeted exercise regimens with a focus on improving balance have been shown to reduce falls [44], and physical therapists can formally test balance and provide targeted exercises for those at risk. Further, the risk of falls may be decreased for some individuals with evaluation and correction of hearing and vision impairment and treatment of neurologic illness. Tobacco should be avoided and alcohol limited to moderate use. Finally, hip protectors incorporated into specially designed underwear were shown to decrease hip fracture by 50% over 12 months in a Danish study of elderly nursing home residents [45] and in a systematic review seemed most effective when implemented in a group setting as part of an overall fall and fracture risk reduction program [46]. Patients’ acceptance and adherence to hip protectors is generally poor, but a patient with a history of hip fracture may be amenable.

**Pharmacologic Therapy**

Pharmacologic treatment for osteoporosis may involve the use of an antiresorptive agent (one that decreases bone resorption, sometimes called an anticatabolic agent) or an anabolic agent (one that stimulates bone formation). In the United States, the only anabolic therapy approved by the Food and Drug Administration (FDA) is PTH(1-34), called teriparatide. The oral bisphosphonates alendronate and risedronate, the intravenous (IV) bisphosphonate zoledronic acid, PTH, and estrogen have been shown in randomized trials to prevent vertebral and nonvertebral fractures. Calcitonin, raloxifene, and the bisphosphate ibandronate have demonstrated the ability to prevent vertebral fractures. Ibandronate has been shown to prevent nonvertebral fractures in a subset of patients with hip T-scores of −3.0 or lower (Table).

**Table. The Effect of Drug Treatment on the Risk of Vertebral, Nonvertebral, and Hip Fractures**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Spine Fracture Reduction</th>
<th>Nonvertebral Fracture Reduction</th>
<th>Hip Fracture Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bisphosphonates</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alendronate (oral)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Risedronate (oral)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ibandronate (oral)</td>
<td>Yes</td>
<td>No*</td>
<td>No</td>
</tr>
<tr>
<td>Zoledronic acid (IV)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>PTH</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*In a post hoc analysis, there was a reduction in nonvertebral fractures in those with femoral neck T-scores below −3.0, but no overall reduction in nonvertebral fractures was demonstrated.

IV = intravenous; PTH = parathyroid hormone.
Oral bisphosphonate therapy. Bisphosphonates impair osteoclast-mediated bone resorption by inhibiting the prenylation of guanosine triphosphate–binding proteins necessary for osteoclast function, resulting in decreased activity and accelerated programmed cell death of those cells. For the prevention and treatment of osteoporosis, 3 oral bisphosphonates are approved by the FDA: alendronate, risedronate, and ibandronate.

Alendronate was the first osteoporosis medication to show a reduction in fracture. In the Fracture Intervention Trial’s vertebral fracture arm, among 2027 women with prevalent vertebral fractures randomized to receive daily alendronate or placebo, alendronate treatment reduced spine, wrist, and hip fractures by 47%, 48%, and 51%, respectively [47]. In the clinical fracture arm of the same trial, randomization of 4432 women without prevalent vertebral fractures showed a similar decrease in first vertebral fracture and a 33% reduction in nonvertebral and hip fractures [48]. A trial of daily risedronate therapy showed a reduction in vertebral fractures by 41% and nonvertebral fractures by 31% in women with prevalent vertebral fractures [49], and in a separate study, daily risedronate reduced the risk of hip fracture by 30% [50]. Daily ibandronate therapy in women with prevalent vertebral fractures reduced new vertebral fractures by 52%; in a post hoc analysis, there was a reduction in nonvertebral fractures in those with femoral neck T-scores below –3.0 but no overall reduction in nonvertebral fractures [51].

The intermittent dosing formulations for these bisphosphonates were FDA-approved based on BMD effects similar to the those of the daily doses used in the fracture trials [51–54]. Alendronate is available as a 10 mg daily or 70 mg weekly preparation. Risedronate is available at 5 mg daily, 35 mg weekly, 75 mg on 2 consecutive days a month, or 150 mg once monthly. Ibandronate is available as a 150 mg monthly dose. In summary, all 3 FDA-approved oral bisphosphonates have been proven to reduce vertebral fracture risk in women with osteoporosis, while there are better data for the reduction of nonvertebral fracture risk with alendronate and risedronate compared with ibandronate.

Before prescribing an oral bisphosphonate, a history of active upper gastrointestinal disease or delayed esophageal emptying should be ruled out, and then precautions should be taken to avoid esophagitis. The tablet should be taken with at least 8 oz of water, and the patient should remain upright after swallowing the medication. Because the bioavailability of the oral bisphosphonates is very poor, they should be taken on an empty stomach for maximal absorption, without food, drink other than water, medications, or supplements for 30 minutes (for alendronate and risedronate) to 60 minutes (for ibandronate) after administration. Bone pain of unclear etiology is a rare complication of bisphosphonate therapy, estimated to occur in 1 in 2000 persons, and while symptoms typically resolve over days to weeks, persistent symptoms have been reported [55].

IV bisphosphonate therapy. Zoledronic acid administered 5 mg intravenously once a year and ibandronate administered 3 mg every 3 months are FDA-approved for the treatment of postmenopausal osteoporosis. The IV formulation of ibandronate was approved by the FDA based on BMD effects statistically noninferior and also superior at the spine and total hip to those of daily oral dosing [56]. Zoledronic acid was tested as an annual 5-mg dose, infused over 15 minutes, in 7665 postmenopausal women with osteoporosis randomized to receive once-yearly zoledronic acid or placebo for 3 consecutive years. The 3-year incidence of vertebral fracture was 10.9% in the placebo group and 3.3% in the zoledronic acid group, a relative risk reduction of 70% [57]. The incidence of hip fracture was 2.5% in the placebo group and 1.4% in the zoledronic acid group, a reduction of 41%. In a separate trial of men and women with recent hip fracture randomized to receive zoledronic acid or a placebo within 90 days after surgical repair of the fracture, new nonvertebral fractures were reduced by 35% in the zoledronic acid group and vertebral fractures were reduced by 46%. In addition, there was a significant 28% reduction in all-cause mortality rate among those who received zoledronic acid [58]. This trial provided some reassurance about the safety of antiresorptive therapy soon after a fracture, as no impairment of fracture healing was noted in those who received zoledronic acid.

Like other IV bisphosphonates, zoledronic acid was associated with transient flu-like symptoms, including pyrexia and myalgia, following its infusion. In the trial of postmenopausal women with osteoporosis, there was an increased risk of serious atrial fibrillation in the zoledronic acid group, although the absolute rates of events were low at 0.5% in the placebo group and 1.3% in the zoledronic acid group [57], and rates of serious and nonserious atrial fibrillation were similar between treatment groups in the trial of men and women with recent hip fracture [58].

Osteonecrosis of the jaw (ONJ) is a rare but feared complication of bisphosphonate therapy, usually with high cumulative IV doses in the setting of cancer therapy. Rates of ONJ with either oral or IV bisphosphonate therapy for osteoporosis appear extremely low, but nevertheless good oral hygiene and regular dental visits should be encouraged. For patients on bisphosphonate therapy for osteoporosis for more than 3 years, the American Society for Bone and Mineral Research has advised that dental implant placement is not contraindicated but that informed consent should be undertaken, and that endodontic treatment is preferable to extraction or periapical surgery when possible [59]. The American Association of Oral and Maxillofacial Surgeons has recommended that for those patients on therapy for more than 3 years, providers
consider the discontinuation of therapy for at least 3 months prior to oral surgery [60], but there are no data on whether this drug-free period alters the incidence or course of ONJ.

**PTH therapy.** Whereas continuous infusion of PTH results in greater resorption of bone than formation, daily intermittent injections lead to proportionally more formation and a net increase in bone mass. Teriparatide, synthetic PTH(1-34), is the only anabolic agent approved by the FDA for the treatment of osteoporosis. In a study of 1637 postmenopausal women with prior vertebral fracture randomized to receive teriparatide or placebo, 20 μg of teriparatide daily decreased the risk of new vertebral fracture by 65% and new nonvertebral fracture by over 53% [61]. The study was terminated early due to contemporary evidence of increased risk of osteosarcoma in rats receiving PTH, but an FDA review of the data concluded that the risk of osteosarcoma in humans was low, and in postmarketing follow-up of more than 300,000 patients worldwide treated with teriparatide, only 1 case of potential but unverified osteosarcoma has been reported [62]. Teriparatide also has proven efficacy in men with osteoporosis [63,64]. Because of lack of long-term data about its use and because the agent is a daily subcutaneous injection and expensive, teriparatide tends not to be used as a first-line drug for osteoporosis but rather is used in men and women with severe osteoporosis, such as those with very low BMD and a fracture or those who fracture while taking a bisphosphonate, or in men and women with significant osteoporosis unable to tolerate bisphosphonate therapy. Following a course of PTH, there is evidence that subsequent bisphosphonate therapy may maintain or increase the bone gained with the PTH, while the discontinuation of PTH without subsequent antiresorptive therapy results in subsequent loss of the BMD gained during PTH therapy [65].

**Raloxifene.** A selective estrogen receptor modulator, raloxifene binds to the estrogen receptor and elicits tissue-specific pro- or antiestrogen effects. In the bone, it inhibits resorption and increases BMD. In a randomized trial of 7705 postmenopausal women with osteoporosis, raloxifene 60 mg daily reduced the relative risk of vertebral fracture by 30% [66]. While the drug increased femoral neck BMD by 2.1% to 2.4%, there was no effect on nonvertebral fracture risk. There was an increased risk of venous thromboembolism and a lower incidence of breast cancer in the women who took raloxifene. Extension of treatment to 8 years demonstrated sustained effects on BMD but did not show a reduction in nonvertebral fractures [67]. Because of the lack of proven nonvertebral fracture reduction, raloxifene may be used best in women with fractures who have contraindications to the more potent therapies, who perhaps also have a compelling desire for breast cancer risk reduction.

**Calcitonin.** Calcitonin is approved by the FDA in nasal spray and daily injection forms for osteoporosis in women at least 5 years postmenopausal. The nasal spray is the preferred route of administration and is well tolerated, the only side effect being nasal irritation. The dose for osteoporosis treatment by nasal spray is 200 IU/day, alternating nostrils with each dose. In a randomized trial of nasal calcitonin, 1255 postmenopausal women with lumbar spine T-score lower than −2.0 who received calcitonin had a 33% reduction in the risk of new vertebral fracture compared with those who received placebo nasal spray [68]. The trial was not powered to study the effect on hip fracture, and only about 30% of the randomized participants completed the 5-year study. Given the lack of proven hip fracture reduction, small effects on BMD, the very high drop-out rate, and inconsistent fracture effects among doses in this trial, calcitonin is typically not a first-line treatment for fracture patients.

**Estrogen therapy.** The Women’s Health Initiative estrogen-progesterone combination trial demonstrated a 34% reduction in hip fractures, a 34% reduction in vertebral fractures, and a 23% reduction in other osteoporotic fractures in postmenopausal women receiving estrogen-progesterone therapy [69]. Similar fracture results were seen in the estrogen-only arm [70]. However, the estrogen-progesterone combination trial showed that the risks of breast cancer, stroke, venous thromboembolism, and possibly coronary artery disease were increased with the estrogen-progesterone therapy. For this reason, and given the safety and efficacy of alternate pharmacologic agents, estrogen is no longer a first-line approach to the prevention or treatment of osteoporosis. Instead, its use is largely limited to treatment of women with vasomotor symptoms in the immediate postmenopausal period.

**Combination therapy.** Whether and how to combine therapies for osteoporosis is an active area of investigation. The combination of a bisphosphonate and either raloxifene or estrogen tends to result in a slightly greater, although not additive, increase in BMD than with a single agent alone [71,72]. In 238 previously treatment-naive women randomized to receive alendronate, PTH(1-84), or the 2 combined, there was no clear evidence of synergy between the therapies [73] and a suggestion that concurrent therapy with a bisphosphonate may impair the skeletal response to PTH, particularly at trabecular bone; these findings were supported by a study of previously treatment-naive men [74]. When women taking chronic alendronate or raloxifene therapy were switched to PTH for 18 months, both groups had an increase in BMD in response to PTH therapy. However, there appeared to be an approximately 6-month lag before BMD began increasing in the alendronate group [75]. There are no fracture data for any combination therapies for osteoporosis.
SECONDARY PREVENTION OF FRACTURES

Summary
Despite the tremendous medical and economic impact of osteoporotic fractures, the majority of patients with fragility fractures do not subsequently receive appropriate evaluation and therapy for osteoporosis. The comprehensive management of osteoporosis includes exclusion of secondary causes of low BMD or low bone quality, initiation of nonpharmacologic therapies, and selection of appropriate pharmacologic therapy. Identification and treatment of patients who have fractured is especially valuable when one considers that clinical trials of osteoporosis medications have shown the most profound fracture risk reduction in that secondary prevention group: for example, when women aged 70 to 79 years with osteoporosis were treated with risedronate versus placebo and monitored for hip fracture, there was an overall relative risk reduction of 40% for those receiving the bisphosphonate, but an impressive 60% relative risk reduction among those receiving the bisphosphonate who had a prevalent vertebral fracture at baseline [50]. Given the very high rate for a subsequent fracture among individuals who have had a fracture, individual clinicians and health systems alike must work to minimize missed opportunities for meaningful secondary prevention of fractures. Any fracture in a postmenopausal woman or older man should be regarded as a sentinel event and should alert the clinician to the need for intervention.

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References


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