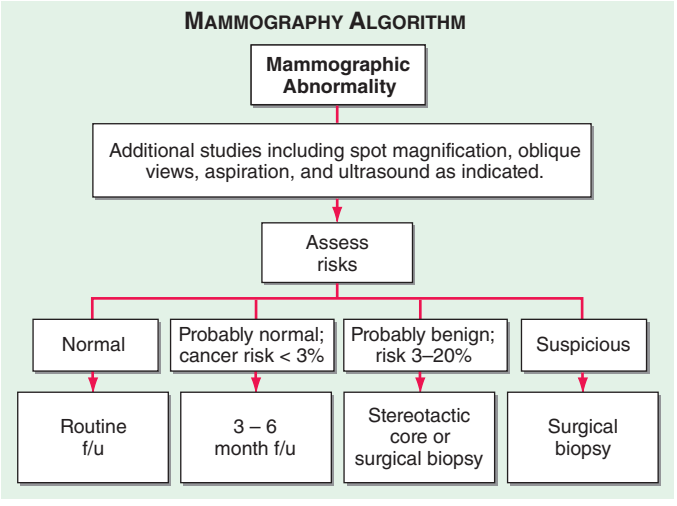

FIGURE 108-4 **Approaches to abnormalities detected by mammogram.**

cancer develops in 1 in every 3000–4000 pregnancies. Stage for stage, breast cancer in pregnant patients is no different from premenopausal breast cancer in nonpregnant patients. However, pregnant women often have more advanced disease because the significance of a breast mass was not fully considered and/or because of endogenous hormone stimulation. Persistent lumps in the breast of pregnant or lactating women *cannot* be attributed to benign changes based on physical findings; such patients should be promptly referred for diagnostic evaluation.

BENIGN BREAST MASSES

Only about 1 in every 5–10 breast biopsies leads to a diagnosis of cancer, although the rate of positive biopsies varies in different countries and clinical settings. (These differences may be related to interpretation, medico-legal considerations, and availability of mammograms.) The vast majority of benign breast masses are due to "fibrocystic" disease, a descriptive term for small fluid-filled cysts and modest epithelial cell and fibrous tissue hyperplasia. However, fibrocystic disease is a histologic, not a clinical, diagnosis, and women who have had a biopsy with benign findings are at greater risk of developing breast cancer than those who have not had a biopsy. The subset of women with ductal or lobular cell proliferation (about 30% of patients), particularly the small fraction (3%) with atypical hyperplasia, have a fourfold greater risk of developing breast cancer than those women who have not had a biopsy, and the increase in the risk is about ninefold for women in this category who also have an affected first-degree relative. Thus, careful follow-up of these patients is required. By contrast, patients with a benign biopsy without atypical hyperplasia are at little risk and may be followed routinely.

SCREENING

Breast cancer is virtually unique among the epithelial tumors in adults in that screening (in the form of annual mammography) improves survival. Meta-analysis examining outcomes from every randomized trial of mammography conclusively shows a 25–30% reduction in the chance of dying from breast cancer with annual screening after age 50 years; the data for women between ages 40 and 50 years are almost as positive; however, since the incidence is much lower in younger women, there are more false positives. While controversy continues to surround the assessment of screening mammography, the preponderance of data strongly supports the benefits of screening mammography. New analyses of older randomized studies have occasionally suggested that screening may not work. While the design defects in some older studies cannot be retrospectively corrected, most experts, including panels of the American Society of Clinical Oncology and the American Cancer Society (ACS), continue to believe that screening conveys substantial benefit. Furthermore, the profound drop in breast cancer mortality rate seen over the past decade is unlikely to be solely attributable to improvements in therapy. It seems prudent to recommend annual or biannual mammography for women past the age of 40 years. Although no randomized study of BSE has ever shown any improvement in survival, its major benefit is identification of tumors appropriate for conservative local therapy. Better mammographic technology, including digitized mammography, routine use of magnified views, and greater skill in mammographic interpretation, combined with newer diagnostic techniques (MRI, magnetic resonance spectroscopy, positron emission tomography, etc.) may make it possible to identify breast cancers even more reliably and earlier. Screening by any technique other than mammography is not indicated. However, the ACS suggests that younger women who are *BRCA1* or *BRCA2* carriers or untested first-degree relatives of women with cancer; women with a history of radiation therapy to the chest between ages 10 and 30 years; women with a lifetime risk of breast cancer of at least 20%; and women with a history of Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba syndromes may benefit from MRI screening, where the higher sensitivity may outweigh the loss of specificity.

STAGING

Correct staging of breast cancer patients is of extraordinary importance. Not only does it permit an accurate prognosis, but in many cases, therapeutic decision-making is based largely on the TNM (primary tumor, regional nodes, metastasis) classification **(Table 108-1)**. Comparison with historic series should be undertaken with caution, as the staging has changed several times in the past 20 years. The current staging is complex and results in significant changes in outcome by stage as compared with prior staging systems.

TREATMENT BREAST CANCER

One of the most exciting aspects of breast cancer biology has been its subdivision into at least five subtypes based on gene expression profiling.

1. **Luminal A:** The luminal tumors express cytokeratins 8 and 18, have the highest levels of estrogen receptor expression, tend to be low grade, are most likely to respond to endocrine therapy, and have a favorable prognosis. They tend to be less responsive to chemotherapy.
2. **Luminal B:** Tumor cells are also of luminal epithelial origin, but with a gene expression pattern distinct from luminal A. Prognosis is somewhat worse that luminal A.
3. **Normal breast–like:** These tumors have a gene expression profile reminiscent of nonmalignant "normal" breast epithelium. Prognosis is similar to the luminal B group. This subtype is somewhat controversial and may represent contamination of the sample by normal mammary epithelium.
4. ***HER2* amplified:** These tumors have amplification of the *HER2* gene on chromosome 17q and frequently exhibit coamplification and overexpression of other genes adjacent to *HER2*. Historically the clinical prognosis of such tumors was poor. However, with the advent of trastuzumab and other targeted therapies, the clinical outcome of *HER2* -positive patients is markedly improving.
5. **Basal:** These estrogen receptor/progesterone receptor–negative and *HER2*-negative tumors (so-called triple negative) are characterized by markers of basal/myoepithelial cells. They tend to be high grade, and express cytokeratins 5/6 and 17 as well as vimentin, p63, CD10, α-smooth muscle actin, and epidermal growth factor receptor (EGFR). Patients with *BRCA* mutations also fall within this molecular subtype. They also have stem cell characteristics.

PRIMARY BREAST CANCER

Breast-conserving treatments, consisting of the removal of the primary tumor by some form of lumpectomy with or without irra-