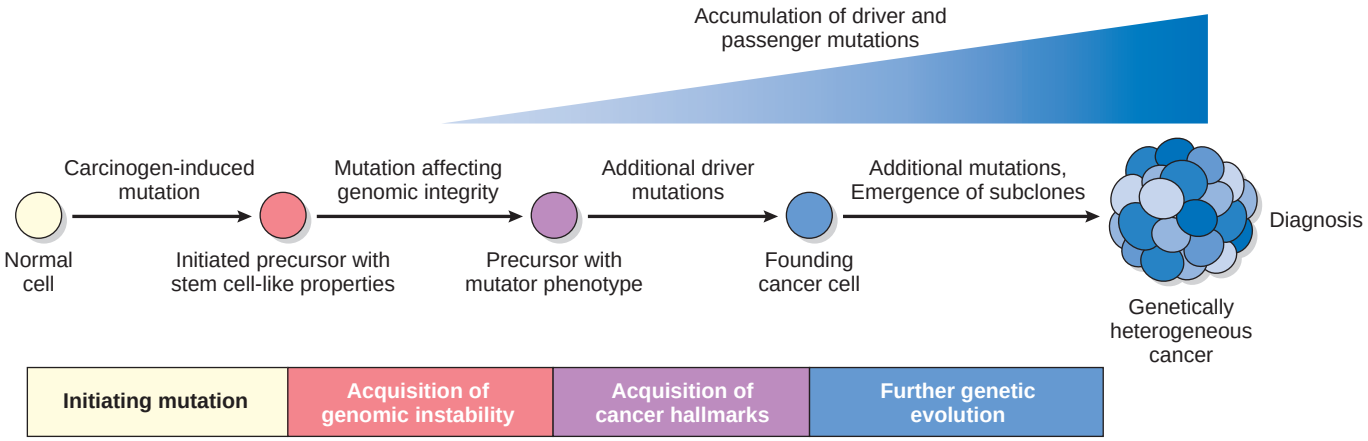

Figure 7-22 Development of a cancer through stepwise acquisition of complementary mutations. The order in which various driver mutations occur in initiated precursor cells is not known and may vary from tumor to tumor. See text for details.

alterations that change the expression and function of key genes and thereby impart a malignant phenotype.

- **Mutations that contribute to the development of the malignant phenotype are referred to as *driver mutations*.** The first driver mutation that starts a cell on the path to malignancy is the *initiating mutation*, which is typically maintained in all of the cells of the subsequent cancer. However, because no single mutation appears to be fully transforming, development of a cancer requires that the "initiated" cell acquire a number of additional driver mutations, each of which also contributes to the development of the cancer. The time over which this occurs is unknown in most cancers, but appears to be lengthy; even in aggressive cancers that clinically seem to appear "out of the blue," such as childhood acute lymphoblastic leukemia, cells bearing initiating mutations may be found in blood samples taken as long as a decade prior to diagnosis. The persistence of initiated cells during this long preclinical prodrome is consistent with the idea that cancers arise from cells with stem cell–like properties, so-called *cancer stem cells*, that have a capacity for self-renewal and long-term persistence.
- **Loss-of-function mutations in genes that maintain genomic integrity appear to be a common early step on the road to malignancy, particularly in solid tumors**. Mutations that lead to genomic instability not only increase the likelihood of acquiring driver mutations, but also greatly increase the frequency of mutations that have no phenotypic consequence, so-called *passenger mutations*, which are much more common than driver mutations. As a result, by the time a cell acquires all of the driver mutations that are needed for malignant behavior, it may bear hundreds or even thousands of acquired mutations.

Once established, tumors evolve genetically during their outgrowth and progression under the pressure of Darwinian selection (survival of the fittest). Early on, all of the cells in a tumor are genetically identical, being the progeny of a single founding transformed cell. However, by the time a tumor comes to clinical attention (generally when it attains a mass of about 1 gm, or about 10^9 cells), it has gone through a minimum of 30 cell doublings. This number is likely a substantial underestimation, because some fraction of cells in virtually all tumors die by apoptosis, and sometimes such cells are numerous. During this process, there is competition among tumor cells for access to nutrients and microenvironmental niches, and subclones with the capacity to overgrow their predecessors tend to "win" this Darwinian contest and dominate the tumor mass, only to be replaced by other, still malignant subclones. This pernicious tendency of tumors to become more aggressive over time is referred to as *tumor progression*. As a result, even though malignant tumors are clonal in origin, by the time they become clinically evident their constituent cells are often extremely heterogeneous genetically, particularly tumors with a mutator phenotype (Fig. 7-22).

A skeptical student might well ask, "How do we know that genetically distinct subclones really exist in any particular cancer?" Supportive data are now emerging from studies of solid cancers such as renal cell carcinoma, in which multiple regions of primary tumors and several different metastatic deposits have been subjected to extensive DNA sequencing (Fig. 7-23). As predicted, two types of mutations were identified in these studies: (1) mutations that were present in all tumor sites tested, which were presumably present in the founding cell at the moment of transformation, and (2) mutations that were unique to a subset of tumor sites, which were likely acquired after transformation during the outgrowth and spread of the tumor. This second type of mutation can be used to create tumor "family trees" showing the genetic relationships of various subclones. Remarkably, subclones within tumors appear to diverge genetically in a fashion that is very similar to the manner in which new species are thought to emerge in complex ecosystems; a cardinal example of the latter are the finches on the Galapagos Islands that inspired Darwin, in part, to propose evolution as the origin of the species. In the case of species, this genetic divergence occurs over a period of many millennia, whereas in tumors, subclones may arise and diverge on a timescale of years, months, or even weeks.

Selection of the fittest cells can explain not only the natural history of cancer, but also changes in tumor behavior following therapy. One of the most profound