

treatments are safe and effective for particular diseases. This is clearly untenable. There are important public health reasons for regulating the ability of companies to promote off-label uses of drugs for which the data have not been reviewed by the FDA. Manufacturers' communications to physicians exist to increase product sales and heavily shape the choices of prescribers. Commercial distortions of the medical literature are well documented, including omission or underemphasis of safety data,¹ presentation of negative or questionable findings about efficacy as being positive,² selective publication of results,³ and industry-sponsored ghostwriting of seemingly academic papers.⁴ The Supreme Court's recent skepticism regarding similar regulation results from the Court's current composition and the political decisions leading to it. Perhaps additional promotion-driven drug debacles that affect public health will help the

Court return to the view that the special complexity and extremely high stakes of decisions regarding medication use — and the associated problems with commercial speech in this area — warrant enhanced government oversight.

Aaron S. Kesselheim, M.D., J.D.

Jerry Avorn, M.D.

Harvard Medical School
Boston, MA 02115
akesesselheim@partners.org

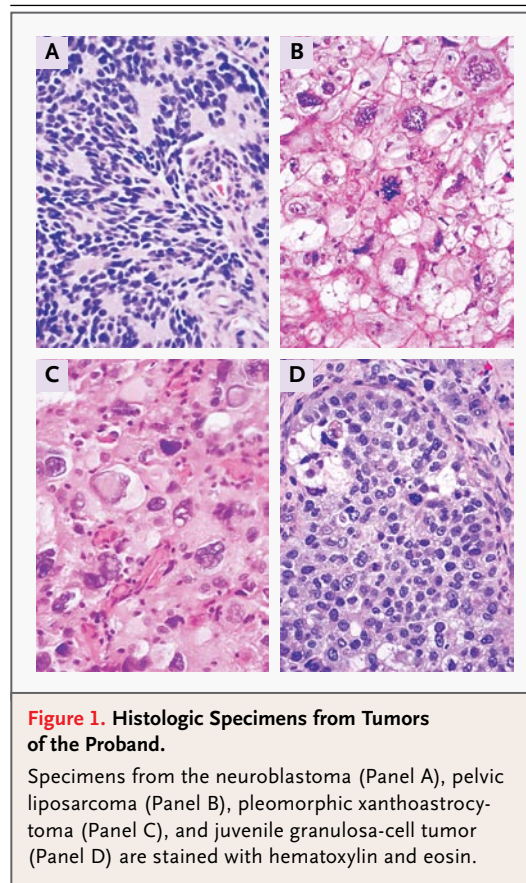
1. Curfman GD, Morrissey S, Drazen JM. Expression of concern reaffirmed. *N Engl J Med* 2006;354:1193.
2. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. *N Engl J Med* 2008;358:252-60.
3. Ridker PM, Torres J. Reported outcomes in major cardiovascular clinical trials funded by for-profit and not-for-profit organizations: 2000-2005. *JAMA* 2006;295:2270-4.
4. Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. *JAMA* 2008;299:1800-12.

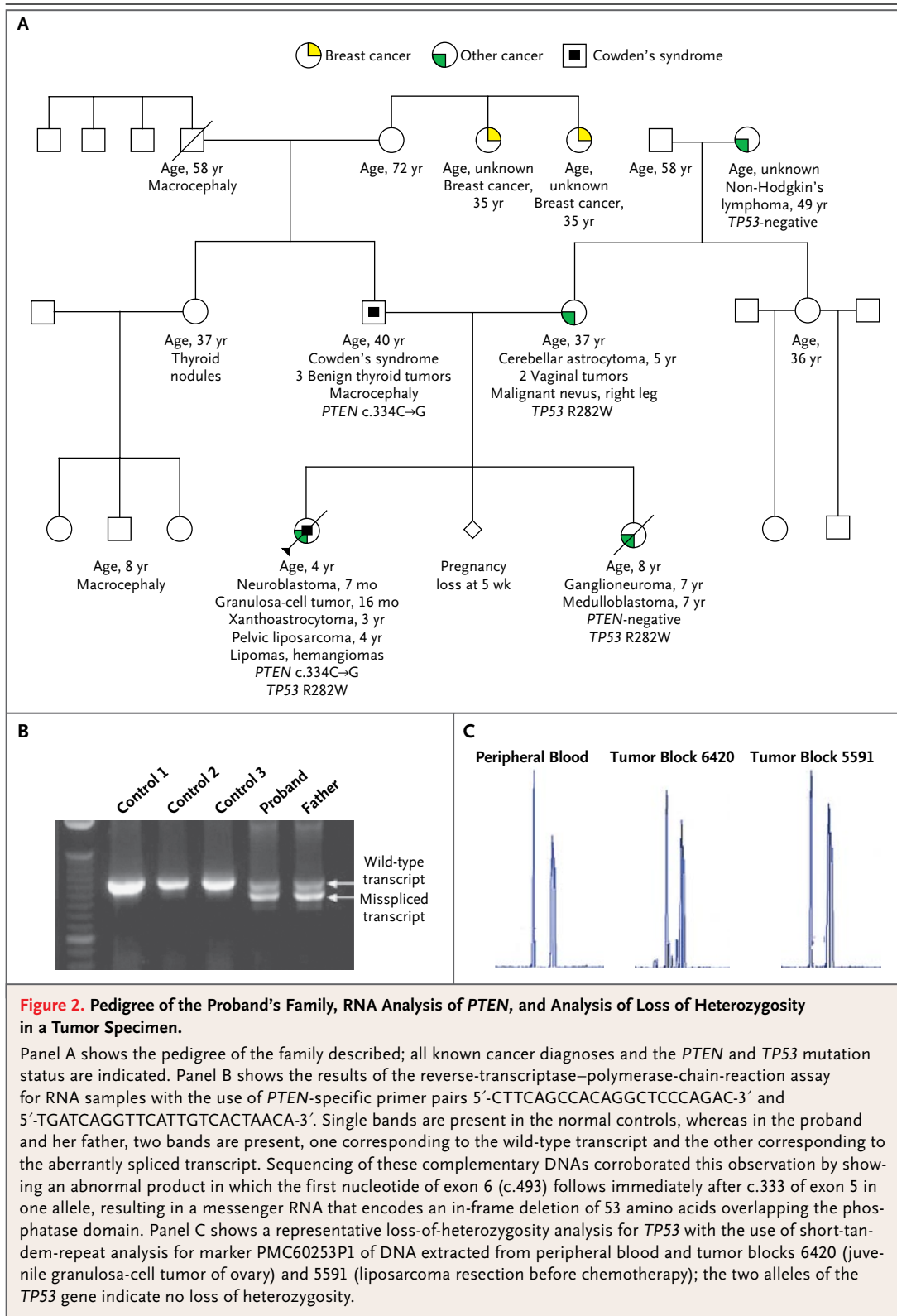
Multiple Tumors in a Child with Germ-Line Mutations in *TP53* and *PTEN*

TO THE EDITOR: *TP53*, a tumor-suppressor gene, is frequently inactivated by somatic mutations in cancer. Inheritance of a heterozygous *TP53* mutation results in the Li-Fraumeni syndrome of a hereditary predisposition to cancer.¹ A germ-line mutation of the *PTEN* gene is associated with Cowden's syndrome of familial susceptibility to multiple hamartomas and to cancers of the breast, thyroid, and central nervous system.² We describe a child who inherited mutations of both *TP53* and *PTEN*.

A 7-month-old girl received concurrent diagnoses of an abdominal-wall lipoma and stage 3 differentiating neuroblastoma; at 16 months of age, a localized, anaplastic juvenile granulosa-cell tumor of the ovary was detected. She also had macrocephaly and hemangiomas. At 3 years of age, a temporal-lobe xanthoastrocytoma developed, and at 4 years of age, she was found to have a pelvic pleomorphic liposarcoma that was metastatic to lung and bone and that was unresponsive to therapy. Histologic analysis of the four tumors revealed extreme pleomorphism and bizarre mitoses with abnormal karyotypes (Fig. 1).

At 7 years of age, the proband's sister received a diagnosis of synchronous anaplastic medulloblastoma and abdominal ganglioneuroma. The father had benign thyroid disease and macrocephaly, and his family history included early-





onset breast cancer in two aunts. The patient's mother had a cerebellar astrocytoma, two vaginal tumors, and a malignant nevus (Fig. 2A).

The germ-line *PTEN* genes of the child and her father had a base change, c.334C→G. Although this change putatively encodes an L112V missense mutation, *PTEN* messenger RNA (mRNA) analysis instead revealed activation of a cryptic splice site (Fig. 2B). The germ-line *TP53* gene in the proband, her sister, and her mother contained an R282W deleterious missense mutation. Thus, the proband had inherited deleterious mutations in both *TP53* and *PTEN*.

In tumors from patients with the Li–Fraumeni syndrome or Cowden's syndrome, there is often somatic mutation or silencing of the second copy of the tumor-suppressor gene.³ The granulosa-cell tumor, xanthoastrocytoma, and multiple liposarcoma samples from our proband revealed no somatic mutations in *TP53* or *PTEN*. Loss of heterozygosity was not detected in *TP53*, but it was detected in *PTEN* in the granulosa-cell tumor and the liposarcoma specimen after chemotherapy (but not in specimens from the initial resection and lung metastasis) (Fig. 2C). The finding that several of the patient's tumors did not have loss of heterozygosity or somatic mutations was also reported for tumors from a mouse model that was doubly heterozygous for *p53* and *Pten* mutations.⁴

The types and numbers of tumors that developed in the proband by 4 years of age are not typical of the Li–Fraumeni syndrome or Cowden's syndrome, and four malignant conditions are expected to develop in only 2% of patients with

the Li–Fraumeni syndrome.^{1,5} This tumor spectrum may reflect the intricate coregulation of the *TP53* and *PTEN* proteins.⁴ Clinically, it may be useful to sequence in parallel multiple cancer-associated genes of patients with unusual cancer phenotypes.

Sharon E. Plon, M.D., Ph.D.

Michael L. Pirics, B.Sc.

Jed Nuchtern, M.D.

John Hicks, M.D., Ph.D.

Heidi Russell, M.D.

Baylor College of Medicine

Houston, TX 77030

splon@bcm.edu

Shipra Agrawal, Ph.D.

Kevin Zbuk, M.D.

Charis Eng, M.D., Ph.D.

Cleveland Clinic Foundation

Cleveland, OH 44195

Madhuri Hegde, Ph.D.

Ephrem Lip-Hon Chin, B.Sc.

Emory University School of Medicine

Atlanta, GA 30322

1. Birch JM, Alston RD, McNally RJ, et al. Relative frequency and morphology of cancers in carriers of germline *TP53* mutations. *Oncogene* 2001;20:4621-8.

2. Sansal I, Sellers WR. The biology and clinical relevance of the *PTEN* tumor suppressor pathway. *J Clin Oncol* 2004;22:2954-63.

3. Knudson AG. Two genetic hits (more or less) to cancer. *Nat Rev Cancer* 2001;1:157-62.

4. Freeman DJ, Li AG, Wei G, et al. *PTEN* tumor suppressor regulates *p53* protein levels and activity through phosphatase-dependent and -independent mechanisms. *Cancer Cell* 2003;3:117-30.

5. Hisada M, Garber JE, Fung CY, Fraumeni JF Jr, Li FP. Multiple primary cancers in families with Li-Fraumeni syndrome. *J Natl Cancer Inst* 1998;90:606-11.

Cytomegalovirus Immunity after Vaccination with Autologous Glioblastoma Lysate

TO THE EDITOR: Glioblastoma is a malignant brain tumor with overall survival rates of less than 3.3% at 5 years.¹ Few effective treatments are available. The durability of a radiographically defined response to treatment is limited, and median survival is less than 2 years.

We are conducting a phase 1 trial of autologous dendritic-cell vaccination as adjunctive therapy in glioma, a study that has been approved by the institutional review board at the University of California, Los Angeles. All patients are treated

with surgery, standard radiotherapy, and temozolomide, followed by vaccination with dendritic cells that are pulsed with an autologous tumor lysate. To date, we have enrolled 14 patients with newly diagnosed glioblastoma (World Health Organization grade IV).

Here we describe Patient 4-908 with glioblastoma who was enrolled in the trial and in whom a robust CD8+ T-cell response to the pp65 immunodominant epitope of human cytomegalovirus (CMV) began immediately after one injection of