NIH's Role in Developing an HPV Vaccine: A Retrospective Portfolio Analysis

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Abstract

The Division of Planning and Evaluation in the Office of Extramural Research conducted a portfolio analysis on the origins of the human papillomavirus (HPV) vaccine, Gardasil, to build a chain of evidence demonstrating NIH's contribution to the research that led to the introduction of Gardasil as a public health measure. We began with a literature review to establish the historical context of the field, identify significant discoveries, and recognize key players. We used federal and international funding databases to identify the research projects that supported pertinent discoveries. We reviewed patent information related to HPV vaccines in the United States Patent and Trademark Office (USPTO) database. We also examined support from NIH and other HHS agencies for clinical trials that may have accelerated Food and Drug Administration (FDA) approval of the vaccine and research projects that contributed to the development of clinical guidelines. Google was useful for locating media articles relevant to the development and clinical implementation of Gardasil. These events mark important milestones in the chain of evidence leading to widespread adoption of the HPV vaccine as a public health measure.

- The research conducted by Harald zur Hausen, who discovered the link between HPV infection and cervical cancer in the early 1980s, was supported by the German Research Foundation
- In the early 1990s, the National Cancer Institute (NCI) awarded approximately $1.8M in extramural funds to investigators at Georgetown University and the University of Rochester who contributed to HPV vaccine development
- NCI intramural funds also supported research that led to HPV vaccine development
- The National Health and Medical Research Council in Australia awarded approximately AU$92,000 to Australian scientists credited, alongside NIH-funded researchers, with discovering the technology underlying HPV vaccines
- As of July 2013, NIH funds contributed to approximately 13 percent of clinical trials initiated since 1995 involving HPV vaccines, and another four percent of trials were funded by other federal agencies
- NIH-supported research contributed to the development of the first recommendation for the use of Gardasil in adolescent females, which was released by the CDC Advisory Committee on Immunization Practices in 2007

Throughout these analyses, the utility of the databases we employed in our research was assessed. Challenges included limitations in the availability of historical funding data and an absence of clear delimiters for assigning funding amounts to specific outputs (e.g. publications, patents, clinical trials, etc.). Together, our efforts demonstrate an approach to portfolio analysis that can provide an in-depth understanding of NIH's contribution to the introduction of a new clinical product.

Background

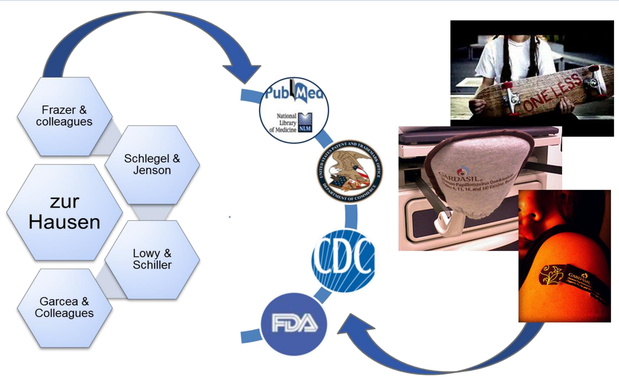


Figure 1. A model depicting the portfolio analysis approach utilized, which involved building a chain of evidence demonstrating NIH's contribution to the basic, translational, and clinical research underlying Gardasil development.

Rationale and Objective

- Human Papillomavirus (HPV) is the most common sexually transmitted infection in the US
- Over 25,000 HPV-attributable cancers are estimated to occur each year in the US
- Two HPV vaccines, Gardasil and Cervarix protect against HPV infection
- Gardasil was the first of the vaccines developed and has been more widely used in the US

The objective of this analysis was to explore the direct and indirect federal support that facilitated the development of Gardasil, its clinical implementation, and its use as a public health measure

Timeline of Key Events

1974: Harald zur Hausen first presented the hypothesis that HPV was associated with cervical cancer at the International Herpesvirus Workshop in Key Biscayne, FL
1983-84: Dr. Zur Hausen identified HPV types 16 and18, the two types of HPV that account for 70 percent of all cervical cancers
1991-1994: Four research teams worked in parallel to discover the technology underlying HPV vaccines. All four groups filed patents for their work causing the USPTO to declare a "four-party interference" and examine the patents filed in greater detail
2005: Merck and GlaxoSmithKline entered into a cross-license agreement allowing each party to license all the necessary patents
2005: Merck applied for priority FDA review for its quadrivalent vaccine, Gardasil
2006: FDA approved Gardasil for use in girls and women through age 26
2008: Dr. zur Hausen received the Nobel Prize in Physiology or Medicine for discovering the link between HPV and cervical cancer
2009: FDA approved Gardasil for use in boys and men ages 13 - 21

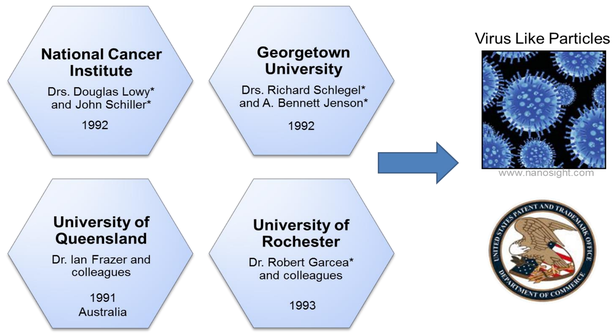


Figure 2. The four research groups credited with developing the virus like particle (VLP) technology underlying HPV vaccines showed that HPV L1 proteins could self-assemble into VLPs and be recognized as antigens by antibodies in human sera. All four groups filed patents for their contribution to VLP development.

Linkage of Publications to Award Data

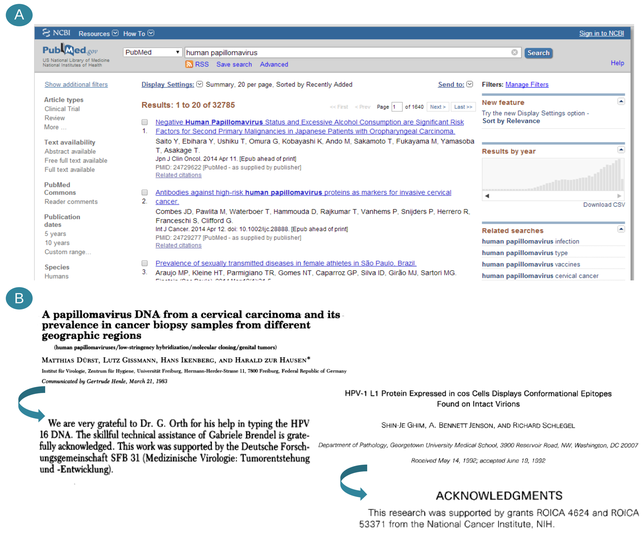


Figure 3. A) PubMed was used to conduct a literature search to establish the historical context of the field and identify key players. B) The acknowledgements sections of two publications describing results pertinent to Gardasil development are shown as examples. The grant information cited in these publications was used to search relevant funding databases to determine approximate award amounts.

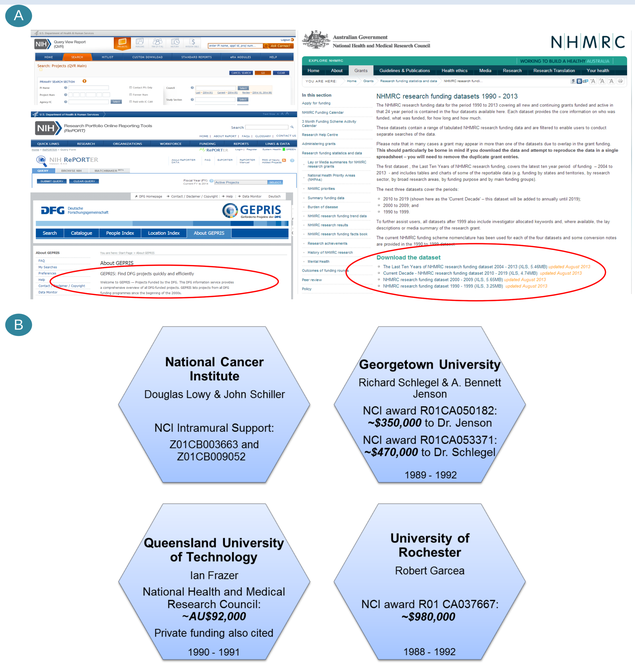


Figure 4. A) Four funding databases (QVR, RePORTER, GEPRIS, NHMRC) were used in this analysis. The GEPRIS database contains funding data for the German Research Foundation since the beginning of the 2000s. The National Health and Medical Research Council provides links to data from 1990 to the present on its public facing website. B) Estimated funding support for key findings published by the research teams credited with discovering VLP technology. Funding counted was all support up to five years prior to the publication date of the article.

Examination of Indirect Federal Support

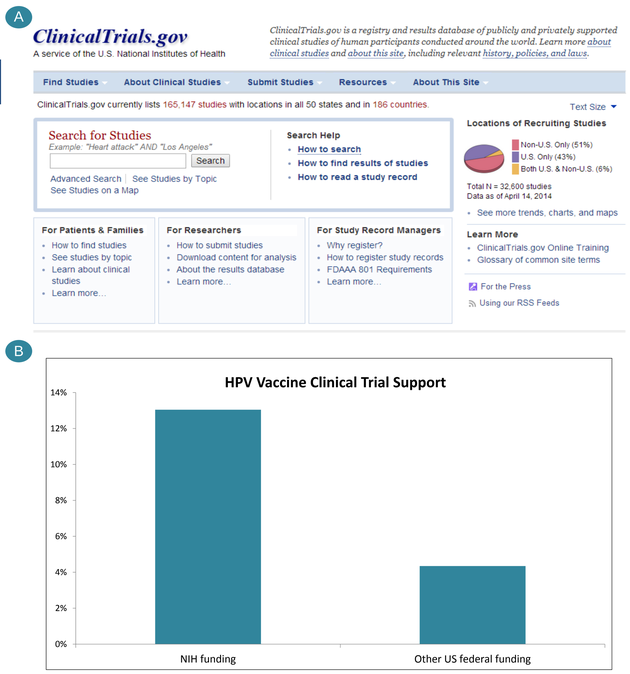
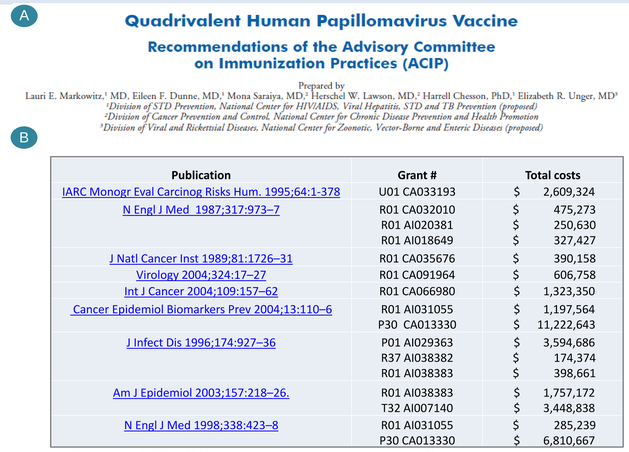


Figure 5. A) ClinicalTrials.gov was used to locate clinical trials on HPV vaccines that were initiated between 1995 and July 2013, which received funding from NIH and/or another federal agency. B) The percentage of trials which received funding from NIH or another federal agency.



Publication	Grant #	Total costs
IARC Monogr Eval Carcinog Risks Hum. 1995;64:1-378	U01 CA033193	$ 2,609,324
N Engl J Med 1987;317:973–7	R01 CA032010	$ 475,273
	R01 AI020381	$ 250,630
	R01 AI018649	$ 327,427
J Natl Cancer Inst 1989;81:1726–31	R01 CA035676	$ 390,158
Virology 2004;324:17–27	R01 CA091964	$ 606,758
Int J Cancer 2004;109:157–62	R01 CA066980	$ 1,323,350
Cancer Epidemiol Biomarkers Prev 2004;13:110–6	R01 AI031055	$ 1,197,564
	P30 CA013330	$ 11,222,643
J Infect Dis 1996;174:927–36	P01 AI029363	$ 3,594,686
	R37 AI038382	$ 174,374
	R01 AI038383	$ 398,661
Am J Epidemiol 2003;157:218–26.	R01 AI038383	$ 1,757,172
	T32 AI007140	$ 3,448,838
N Engl J Med 1998;338:423–8	R01 AI031055	$ 285,239
	P30 CA013330	$ 6,810,667

Figure 6. A) The CDC ACIP recommendation for the use of Gardasil in girls and adolescent women was issued in 2007. B) The references cited in this guideline were traced. Shown is a representative list of references in the ACIP recommendation which cited an NIH grant. Also included is an estimation of total costs of each award cited. Funding counted was all support back to the previous competing year prior to the publication date of the article.

Exploration of Media Articles

Figure 7. A) Media articles and peer-reviewed journal articles published in 2007 – 2012 discussed some of the controversies associated with Gardasil. B) A graph displaying the sales reported by Merck from 2008 – 2013. This graph is an updated version of a similar graph displayed in the media article shown in (A) titled, "The Gardasil Problem: How the U.S. Lost Faith in a Promising Vaccine."

Conclusions

- PubMed was critical in establishing an historical context of the field and identifying key discoveries. Challenges include:
  - Significant effort in gaining knowledge of the field and historical context
  - Historical publications not always available online or archived
- Funding databases were useful in approximately allocating award amounts to discoveries. Challenges include:
  - Limited availability of historical data
  - Grant citations not always accurate
  - Limited availability of private funding data
  - Absence of clear delimiters for assigning funding amounts
- ClinicalTrials.gov was very user-friendly, no significant challenges noted
- Google searches were utilized to locate media articles, which provided social context to the issues surrounding the clinical implementation of Gardasil
- USPTO.gov was not found to be user-friendly and was not used extensively for this analysis