BUILDING A BUSINESS

Differentiated dollars

Building your startup with venture philanthropy investment.

Disease-focused foundations have used venture philanthropy (VP) for decades to develop interventions that have patient impact and generate revenue to support their mission. We articulate the distinguishing motives and features of VP funds and their distinct role in the life sciences innovation ecosystem. In particular, we focus on how entrepreneurs and VP funds can work together to help patients and generate economic value. We recommend that entrepreneurs seeking VP support understand a fund's mission and objectives, and position themselves to fit the fund's strategic and financial portfolio needs. Finally, we provide case studies of three specific initiatives — the JDRF T1D Fund, targeting type 1 (juvenile) diabetes; MPM Capital's Oncology Impact Fund; and the American Heart Association's Cardeation Capital — to showcase these efforts and benefits in practice (Box 1 and Supplementary Note).

VP has been a key impact investment vehicle in the life sciences for more than 20 years. Over this time, impact investment in the life sciences has also evolved to include new investment approaches such as 'impact funds' (funds with objectives other than or in addition to financial performance, such as environmental impact, greater sustainability and good corporate governance, and where a portion of the fees and or gains may be used to support nonprofit activities).

'Traditional' VP is a funding model in which nonprofit organizations attempt to advance their mission by using donated funds to make equity investments in a for-profit company. This differs from non-dilutive funding such as research grants, which typically do not involve an equity position. In some cases, VP investments have the potential to generate financial returns that can then be reinvested to continue to support the organization's mission. However, these returns are not shared with the individuals who contributed the capital. In contrast, impact funds return a share of the investment gains to the contributor of capital while simultaneously donating a portion of the profits or fees to a nonprofit entity.

VP is a large and growing source of funding for biotech startups. From 2002 to 2017, philanthropic investments in healthcare R&D have increased from $520 million to $2.6 billion in the United States. (We were unable to find comparable global data.) This is equivalent to an 11.2% compound annual growth rate (CAGR; Fig. 1a,b). This has outpaced investments from industry, which posted a 6.1% CAGR from 2002 to 2017, and also from the US federal government, which posted a 1.8% CAGR from 2002 to 2017 (Fig. 2).[7,8] Over this period, VP has increasingly become a major driver of innovation, particularly in therapeutic areas requiring 'long shot' investments in volatile capital markets that may not be attractive to typical institutional investors.

Driving the growth of VP is a proliferation of disease-focused foundations (DFFs). At present, there are more than 16,150 DFFs in the United States, and these entities have over $25 billion in combined annual revenue and $40 billion in combined assets[1].

DFFs are strikingly diverse in scope and mission, but they can be loosely grouped into two principal types: those focused on single indications, such as the Cystic Fibrosis Foundation, JDRF or the National Breast Cancer Foundation; and those focused on multiple related indications, such as the American Cancer Society. Regardless of their scope, DFFs are founded to support patients and improve their quality of life. Some DFFs accomplish these goals by offering community support or by raising funds to support patient financial needs. Other foundations take a more active approach in developing programs that improve disease understanding and therapeutic development.

DFFs may also provide support to academic researchers and businesses in the form of cash grants that support R&D. This funding can extend from early-stage, preclinical basic science to the development of novel endpoints in clinical trials. This funding typically comes with 'no strings attached,' or a modest royalty tied to patents generated with the funding.

However, over the past 20 years, some foundations have transitioned from mainly giving grants to support early-stage research to also becoming active investors in startups focused on their disease area. This is especially true for diseases that have historically been unattractive to for-profit venture capital (VC), such as rare and ultra-rare diseases. In particular, VP opens opportunities to share in the success of the entities receiving financial support, shape the commercial landscape of their indication, and lower barriers for additional for-profit dollars to invest in the space. By tying investment to an equity position, VP can provide novel revenue streams that support other aspects of an organization's mission — such as financially supporting patients or raising disease awareness — while simultaneously supporting novel medical advances. Given that VP is still in its infancy, there is little systematic data on financial returns, but many of the organizations most actively engaged in VP do not measure their performance solely by traditional financial metrics such as return on investment. Instead, many measure success by impact on patient lives, and by that metric, there are a number of extraordinary successes, including the VP investments of the Cystic Fibrosis Foundation (CFF) in Vertex Pharmaceuticals and other related biopharma companies[2]. But in this case, as in many other biomedical contexts, significant impact on patient lives also means highly attractive returns for investors.

Benefits to partnering with venture philanthropy funds

Entrepreneurs obtain three principal benefits when partnering with VP funds.

Access to broader foundation resources. VP funds are affiliated with DFFs that typically have deep scientific roots in their focus area. Specifically, we are unaware of any DFF with a VP fund that does not also have some form of scientific grant vehicle. In turn, these DFFs have a scientific advisory board staffed with key opinion leaders in the space to inform grant strategy. VP funds can tap into these relationships and engage these key opinion leaders as research collaborators and trial investigators. Additionally, many foundations, particularly for rare diseases, establish patient registries or biobanks that tap into their membership

Box 1 | Examples of successful VP collaborations

JDRF T1D Fund. The JDRF T1D Fund launched in 2016 and is a focused effort to catalyze and accelerate for-profit VC investment in the type 1 diabetes (T1D) space. As such, the fund has a focus on strategic investments that will increase for-profit VC leverage. In 2017, T1D Fund made an investment in SQZ Biotech to support the application of its platform technology to juvenile diabetes. This investment allowed SQZ to have the economic flexibility and access to T1D expertise to justify launching a program that added to its value-creation capability and further validated its platform.

This investment also opened doors for the T1D Fund to increase innovation in its target indication. SQZ's principal venture capital support at the time came from Polaris Partners, a $4 billion for-profit fund with more than 600 investments in technology and life sciences companies[4]. Following this investment, Polaris supported the T1D Fund investment in Pandion, which the T1D Fund backed in 2018. Pandion subsequently launched an IPO in 2020 and was acquired by Merck & Co. in 2021 for $1.85 billion[5]. These were Polaris's first two portfolio companies to have any T1D assets. In 2021, the T1D Fund and Polaris both participated in the series C round for Seraxis Therapeutics, which has a lead asset in T1D for beta cell replacement therapy. This was Polaris's first investment of any kind in a company centered on T1D and its third investment related to T1D in four years, showcasing how VP contributions can have a multiplicative effect in catalyzing for-profit funding in an indication.

MPM Oncology Impact Fund. MPM is a for-profit VC fund that has raised approximately $4.7 billion across 12 funds since 1997 and has made more than 200 investments resulting in over 100 IPOs or acquisitions. MPM is unique among its peers in having multiple oncology-focused funds with philanthropic components. In 2016, MPM partnered with UBS to launch the first of its oncology impact funds (OIF 1). Additionally, in 2020, MPM launched its Oncology Innovations Fund in partnership with Dana-Farber Cancer Institute. The OIF is an innovative effort to blend for-profit investing with philanthropy. MPM manages capital raised from clients of UBS Wealth Management and donates 20% of its performance fee to the American Association for Cancer Research (AACR) and UBS's Optimus Foundation, and has committed to donating 1% of royalties earned on future products from its portfolio companies to the same. The OIF always co-invests with other MPM funds (most notably its BioVentures funds). This brings extra capital to startups, allowing the fund to engage in larger scale follow-on investments. The fund has made numerous successful investments, such as the one in ElevateBio. In 2019, OIF was a lead investor in ElevateBio's $150 million series A. The company has since gone on to raise a $170 million series B in 2020 and a $525 million series C in 2021. As of March 2021, seven OIF companies have gone public and several more have reported positive early clinical data.

Due to the fund's royalty structure, as the fund matures, the value of donations has the potential to increase significantly. In the case of AACR, these donations go directly to funding early-stage oncology science[6]. This helps create a virtuous cycle whereby MPM might one day invest in a company whose science was established with the help of its donations.

American Heart Association's Cardeation Capital. Cardeation Capital was launched in 2018 as a $30 million venture fund in partnership between UPMC Enterprises, Philips and the American Heart Association. The fund is managed by a third party, Aphelion Capital, which has its own for-profit products. Cardeation Capital focuses on device and digital health companies in the cardiac and brain health space. The fund's objective is to maximize its financial returns while supporting promising companies and entrepreneurs aligned with the Association's mission. Cardeation Capital's partners provide complementary and mutually reinforcing skills that unlock value for portfolio companies. For example, UPMC provides a payer and provider perspective when assessing and advising companies. UPMC is also able to act as a source of potential investment targets. At the same time, Philips can provide market, commercialization and technical expertise. Philips can also serve as a potential exit opportunity for investments. Additionally, the Association provides scientific expertise and access to key opinion leaders. Finally, Aphelion has expertise nurturing companies and advising on business operations and financial structuring.

This breadth of resources provides significant support to portfolio companies. This attractiveness, coupled with the focus on devices and technology, allows Cardeation Capital to invest in companies across broad stages of development, including some that already have revenue. Furthermore, as a result of its alignment with the Association's mission, Cardeation Capital is focused on patient impact and tracks lives affected as a key performance indicator alongside traditional metrics of financial success.

networks. For example, the CFF established a registry in 1986, which provides them with extensive information on disease progression, symptoms, quality of life, and treatment efficacy. For large DFFs, these registries may encompass almost the entire patient population; as of 2019, the CFF registry has more than 30,000 participants[3]. These registries provide fertile ground for recruiting clinical trial participants in challenging indications with small patient populations. Ultimately, all this information is integral for drug developers, regulators, providers and patients.

Willingness to invest in high-risk areas. VP funds are in a unique position to harbor financial risk in the drug development landscape. Because they do not return proceeds from gains to their capital contributors, VP funds may have lower thresholds for expected returns and exit timing. In turn, they may be more willing to invest in assets or areas than other investors, who may have greater pressure to provide returns in a defined timeline. This difference is particularly critical for entrepreneurs in historically underfunded disease areas, such as rare diseases and neglected tropical illnesses, or with higher-risk assets, such as novel mechanisms of action. Specifically, some entrepreneurs who prefer to have an impact rather than maximize valuation at exit may find their scientific agendas are better aligned with the objectives of some VP funds.

Concept validation. Beyond being an independent source of capital and resources, support from an established VP fund may provide a credible signal to other investors. This added value can manifest itself in several ways. First, most VP funds

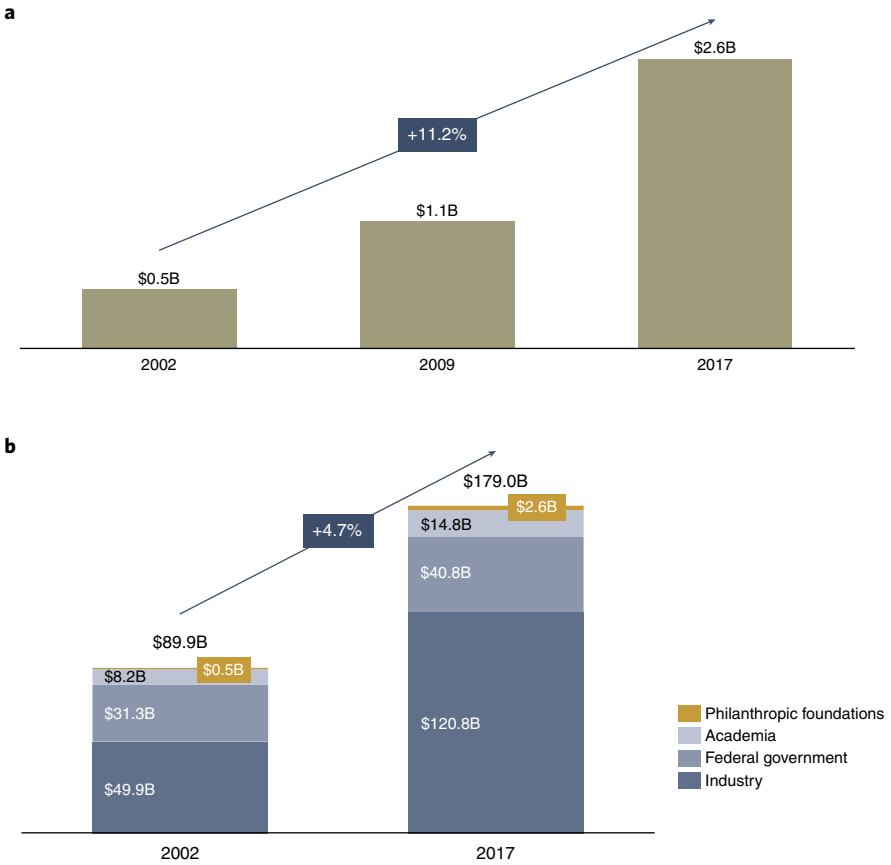

Fig. 1 | Growth in US disease foundation research investments and in principal sources of US healthcare R&D investment, 2002–2017. a, Growth in US disease foundation research investments. **b**, Growth in principal sources of US healthcare R&D investment. Adapted from Research America, 2002 and 2019. Arrow shows CAGR across the span shown; B, billion.

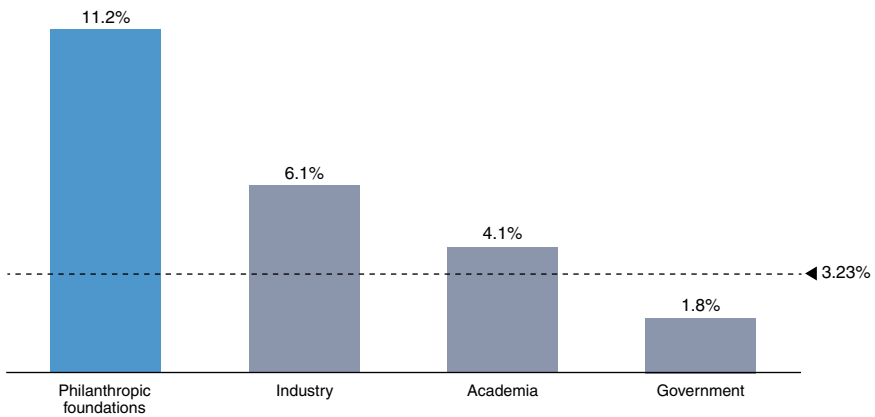

Fig. 2 | US R&D investment growth rates, 2002–2017. Adapted from Research America, 2002 and 2019. Dashed line shows the average inflation rate over the period 1914–2021.

have established relationships with other for-profit funds that can be drawn into an investment syndicate. Second, VP funds often also have industry relationships at established pharma companies that could provide exit opportunities, technical support or other resources. Lastly, VP funds can provide opportunities to accelerate value creation by supporting follow-on clinical development in indications that an entrepreneur may not have considered without dedicated economic support.

Key considerations for partnering with a VP fund

Biotech founders interested in partnering with a VP fund need to consider the following four issues: getting the VP's attention, making sure that there is sufficient alignment of objectives, ensuring proper positioning of the investment opportunity, and determining investment sizing.

Getting on the VP radar. Funds typically source their deal flow from a mix of personal relationships with proven entrepreneurs or successful for-profit funds and relationships with academic medical centers or physicians.

For some entrepreneurs, such as those already operating with grant funding from a foundation, these connections may be clear and actionable. You might reach out to a grant administrator or foundation contact for an introduction, for example. However, for many, more effort may be required to engage a VP fund. Many entrepreneurs affiliated with research universities, especially those starting their first venture, would likely be best served leveraging their institution's resources as a starting point. In particular, entrepreneurs in academia may consider seeking the support of their technology transfer office or engaging peers with established ties to a foundation to facilitate an introduction. A number of institutions have even launched VP initiatives of their own to support faculty and student startups; examples include the Dana-Farber Cancer Institute, Harvard, the Massachusetts Institute of Technology (MIT), the University of California Berkeley and the University of Pittsburgh Medical Center. Many of these opportunities may also be available to established companies outside academia that may still have leadership team members affiliated with their parent institutions. Beyond leveraging their academic or personal connections, seasoned entrepreneurs may also develop connections to VP funds via their existing or previous investors. (This option will be unavailable to first-time entrepreneurs.) Specifically, for-profit investors looking to form a syndicate may draw a VP fund into an opportunity if they feel there is a strong alignment to the VP's mission. A leading example is Deerfield Management, a for-profit healthcare investment company that has established partnerships with 16 academic institutions in which they provide funding and commercialization expertise in exchange for access to intellectual property and academic talent.

Articulating and aligning position, mission and goals. VP organizations are inherently mission driven. For many VP funds, this means understanding the fund's objectives within the target indication. There are several 'flavors' of focus, including generating returns for the parent foundation, attracting for-profit capital into a space to grow the ecosystem, and investing only to enable proof of concept. For an entrepreneur, this insight can help identify themes to highlight or underscore during conversations. You might want to rely more heavily on financial metrics, show a willingness to 'play ball' with a syndicate, or articulate the necessary hurdles to clear to reach a pivotal trial.

The most successful entrepreneurs will also define how collaborating with a VP fund will unlock value and opportunities for both investors and patients that are not available via other channels or sources of capital. By articulating to their existing investors — and to patient advocacy groups considering the VP route — why VP dollars are superior to the next best available dollar from another source of capital, entrepreneurs can help ensure there is mutual alignment on the balance between patient impact, capital returns and resource allocation.

Positioning an opportunity for a VP fund. Once entrepreneurs are able to articulate how their venture will benefit from VP resources and align with its organizational mission, they should pivot to addressing a fund's investment goals.

VP investments can be thought of as fitting across two principal axes (Fig. 3). The first axis is the financial spectrum. These investments are made predominantly for their potential financial return. This is not to say that they are not aligned with the organizational mission — these deals may just be in companies with lower risk, more diverse portfolios or a less transformative innovation. This financial return is almost always plowed back into other investments or the parent organization. The second axis is the alignment with the fund and its organizational strategy and mission. Investments that skew toward the strategic are made because they may significantly advance the field, have very high risk, further a key relationship or would die without foundation support. While these investments are made because they further the organization's mission, their risk makes it challenging for funds to exclusively execute purely strategic deals. While funds aspire to make investments that are both highly strategic and yield a high financial return, the availability of deals and the state of market development may preclude this. In turn, funds must balance their mix of strategic and financial investments as a form of portfolio management.

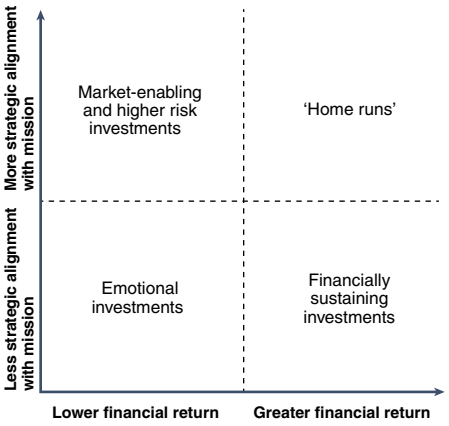

Fig. 3 | Venture philanthropy investment spectrum. Venture philanthropy investments generally fall into one of four buckets depending on their financial potential and alignment to the philanthropic mission.

An additional consideration that influences investment decisions is the stage of asset development. The majority of the funds we engaged with prioritized funding companies at the seed stage or perhaps series A. This is both a function of maximizing the impact of the scale of the deployments and an effort to draw in additional for-profit dollars at a critical juncture. In particular, given the relatively modest scale of the average deployment, these early rounds allow VP funds to take meaningful equity stakes. Moreover, they also engage in follow-on investments in later rounds provided that they do not overly concentrate the fund in any single investment. They make such investments not just to avoid being diluted; if they continue to believe in the therapeutic potential of the program and if, for whatever reason, the company has difficulty in raising capital to continue its development, the VP will step in to keep the program from languishing.

VP funds may also invest in an established company if the capital will spur incremental development in the target indication using the company's platform or technology. While investing in established companies may require writing larger checks or may require investor connections, it provides many benefits to the VP fund. These companies should be relatively low risk, since their lead assets often have some element of platform validation. Also, since they are more mature than seed-stage companies, they may produce returns sooner. This shift in return and risk profile could mean that some of a philanthropy fund's most successful exits could also be investments that the market may not consider as explicitly aligned to the foundation's mission.

Investment sizing. The scale of individual capital deployments will vary on the basis of the size of the fund and magnitude of the opportunity. However, we consistently heard that $150,000 to $250,000 was the bare minimum needed to make an investment 'worthwhile' to the stakeholders, including the startup. For most of the individuals we spoke with, a typical range for investments was $1 million to $5 million. On the high end, we heard funds would seek to avoid concentrating more than 10% of total fund assets in any one investment. For most of the groups we spoke to, this threshold topped out at around $10 million although this varied if an exceptional opportunity emerged. At this scale, VP funds are seldom the sole or lead investor in a given round and instead work in a syndicate with other stakeholders, such as angel investors or for-profit VC firms.

Conclusion

VP has become an important mechanism for foundations to achieve their mission and support life sciences innovation. Moreover, VP provides a meaningful suite of tangible resources, valuable investment capital and proof-of-concept validation to nascent biotech ventures. As made evident by the impact of the T1D Fund, MPM Oncology Impact Fund and Cardeation Capital, collaboration with a VP fund can alter the trajectory of a venture or even a therapeutic area. To promote VP interest, entrepreneurs should identify how their venture might align with a fund's mission and investment objectives. This may require leveraging academic, personal and investor connections to directly engage with funds.

There are, however, three situations for which VP is not a good fit. First, the chances of misaligned expectations and disappointment are high if the VP fund does not have expertise structuring and evaluating investments or a clear understanding of the respective roles they are expected to play in relation to other stakeholders such as syndicate partners and the founding team. Second, entrepreneurs may find the opportunity cost of pursuing VP funding relative to for-profit channels prohibitive. For example, VP funding could be less desirable if it comes at the cost of a

transformative lead investor that is unwilling to play as part of a syndicate. Third, VP may be less attractive if the capital comes with constraints around commercialization strategy such as product pricing.

Successful VP requires a keen awareness by all stakeholders of how philanthropic resources are integral to simultaneously enabling a startup's success and achieving the philanthropy's mission. Once the entrepreneur and philanthropist can articulate and agree on how the venture's goals align with the fund's mission, they can jointly determine whether a venture may be best positioned as strategically or financially valuable to the fund. ❐

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Competing interests

A.W.L. is co-founder of QLS Advisors, LLC, a healthcare analytics and investment advisory company. A.W.L. also invests in and advises a number of biopharma companies that may collaborate with venture philanthropists (the complete list of his investments and advisory positions is available on his website at https://alo.mit.edu/). A.W.L. is an advisor to the American Cancer Society's BrightEdge Impact Fund, a venture philanthropic organization, and the National Center for Advancing Translational Sciences, a government organization that collaborates with venture philanthropic organizations. A.W.L. has also collaborated with other venture philanthropic organizations on prior research and case studies, including the Cystic Fibrosis Foundation and the National Brain Tumor Society. D.L.A. reports no competing interests.

Additional information

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