

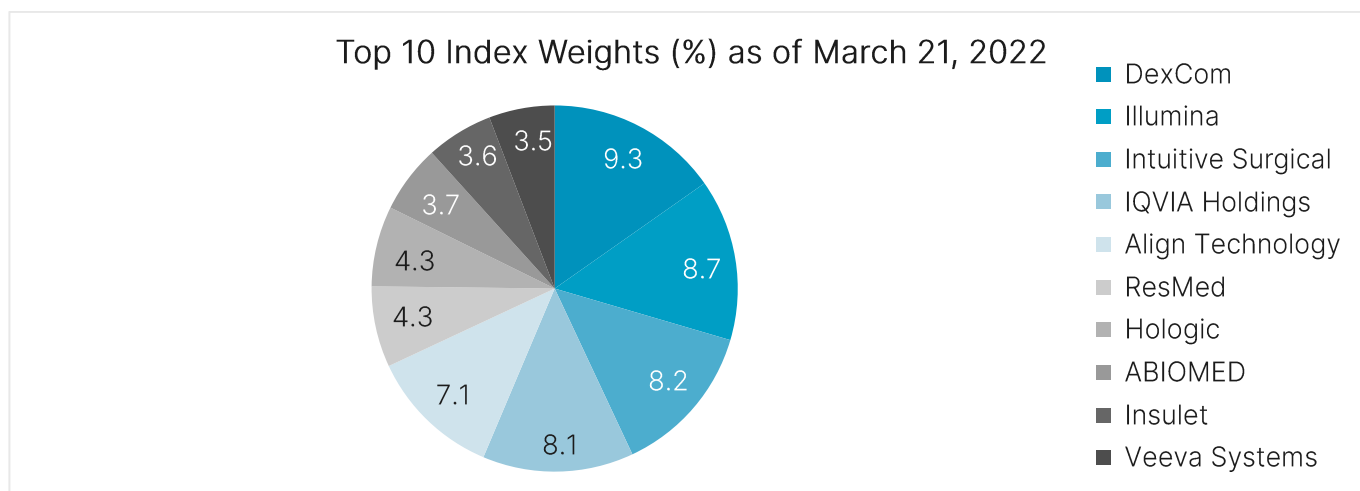
The Nasdaq Lux Health Tech Index: Tracking A New Age of Healthcare Disruption & Digitization

Mark Marex, Director of Index Research & Development

The Nasdaq Lux Health Tech Index™ (NQHTEC™) was launched on July 19, 2021 in partnership with Lux Capital, an emerging science and technology-focused venture capital firm based in New York. Leveraging Lux Capital's more than 20 years of experience investing in disruptive private companies, Nasdaq Index R&D collaborated in the development of NQHTEC to further expand Nasdaq's suite of technology-forward, thematic indexes. The partnership's primary goal was to construct a new, differentiated benchmark of publicly-listed companies that are leading the integration of cutting-edge technology across numerous areas within the healthcare industry. The profile of index constituents spans across biotech, medical devices, software, healthcare services, and research/diagnostic tools, offering investors exposure to key areas of health technology such as genomics, molecular diagnostics, cell therapy, and digital health. As the broader healthcare industry reacts to technological innovation, NQHTEC is well-positioned to offer investors a unique and compelling solution for tracking this highly relevant and exciting theme.

NQHTEC's relatively straightforward methodology employs modified market cap-weighting (8% capping for the top 5 constituents, with the rest capped at 4%) on a semiannual rebalance/reconstitution schedule. Constituents must be listed on a Nasdaq Index Eligible Stock Exchange, and are required to meet minimum thresholds for market cap (\$500M) and liquidity (\$3M average daily trading volume over the last 3 months). In addition to determining index eligibility based on a company's business model, product mix, and R&D focus, Lux Capital also screens new index additions for revenue growth (10% in each of the most recent two fiscal years) and ongoing index membership (7% growth in one of the last two fiscal years, unless a constituent's market cap has reached \$50B). Let's review NQHTEC's holdings and recent performance before digging into thematic exposures and the overall investment case.

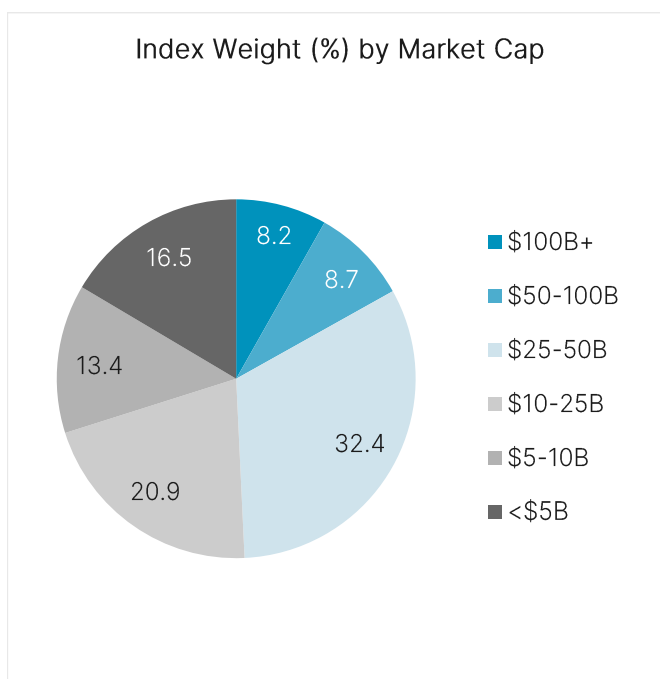
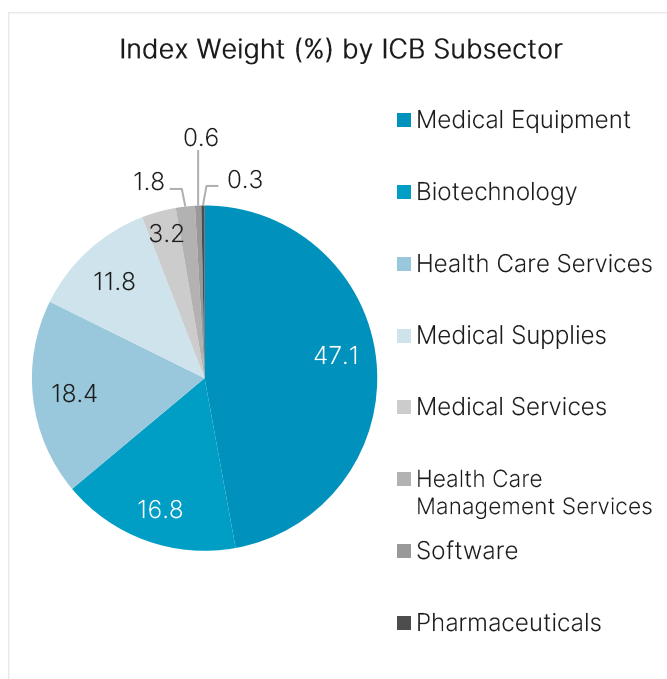
Current Composition



Of the 59 constituents in NQHTEC, the top 10 represented 61% of the index weight as of the most recent reconstitution on March 21, 2022. The top 5 names represented approximately 41%, while the top 20 represented 82%. The largest was DexCom (US: DXCM) at 9.3%, while the largest by pure market capitalization was Intuitive Surgical (ISRG). The average full-year 2021 price return for the top 10 was 19.7%, vs. 53.6% in 2020.

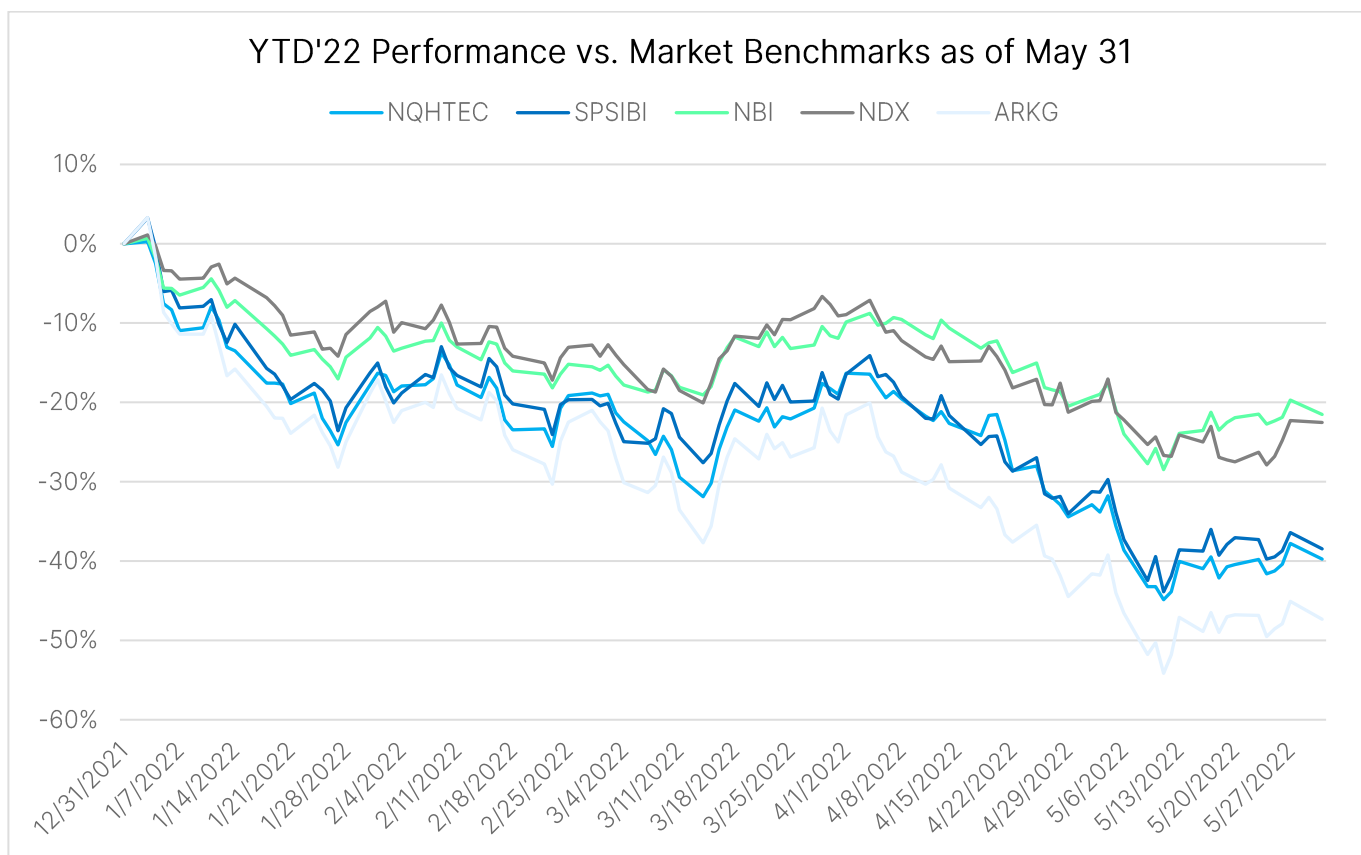
In terms of market capitalization for the overall group, the average was \$11.1B, while the weighted average was \$30.2B (as of March 21, 2022). The median was only \$2.9B, and the range from largest to smallest was \$102.8B. The majority of index constituents (38) had market capitalizations under \$5 billion, contributing 16.5% of index weight; companies with market caps between \$10-50 billion contributed just over half of aggregate index weight. Only two constituents commanded market caps in excess of \$50 billion.

In terms of geographical diversity, NQHTEC's constituents are mostly located in the US, reflecting American dominance in healthcare innovation. Only four constituents are internationally domiciled, for now; the index may very well expand in this regard, as has been observed within the global biotech industry in recent years. In terms of strict subsector classifications, Biotechnology was the second largest at 16.8% of index weight, far smaller than Medical Equipment at 47.1%. Note that Pharmaceuticals barely registered at all, with only one constituent.



Recent Performance

YTD performance through the first five months of 2022 has been challenging, with NQHTEC down nearly 40% amid exceptionally negative macroeconomic headlines around high inflation, rising rates, and Russia's invasion of Ukraine. Its performance was more or less in-line with other indexes tracking companies engaged in healthcare innovation such as the S&P Biotechnology Select Industry Index (SPSIBI), which finished the month of May down 38.5% YTD. The Nasdaq Biotechnology Index™ (NBI™) fared better, down only 21.5%. ARK Investment's Genomic Revolution ETF (ARKG) lost 47.3%, bringing the cumulative drawdown from its peak in early February 2021 to more than 70%. It has been a rather protracted period of weakness not only for Biotech, but several other high-growth areas of the equity market within Technology and Consumer Discretionary, with the Nasdaq-100® (NDX™) down 22.5% YTD – the worst start to a year in two decades.



The reasons for the decline tend to offer investors little satisfaction: interest rates are rising, which puts downward pressure on growth asset valuations. Of course, the Fed has little choice but to respond to elevated inflation trends given its legal mandate; it will likely raise rates until inflation cools to a level that is acceptable, currently estimated around 2-3% annualized. Yet there is little concrete evidence for *why* a company like Intuitive Surgical (ISRG), which has enough cash on hand to cover its long-term debt by 63 times (per Factset as of year-end 2021), should be down 37% YTD. Their 2021 full-year revenues grew 31%, and their net income jumped by 61%. Even if the Fed raises rates by 300 basis points over the course of the next two years – back to levels last seen just a few years ago – what fundamental impact will that have on ISRG’s revenue growth trajectory and their profitability? Healthcare is (mostly) not a discretionary expense, and demand for their cutting-edge surgical equipment is arguably as inelastic as for food and shelter. The market is not always right about valuations, even when the broader trends make some amount of sense.

Thematic Exposures & Key Disruptive Technologies

Thus far we have discussed index composition at a high level, in terms of ICB subsectors, company market caps, and portfolio concentration. What about the thematic exposures of NQHTEC? What types of groundbreaking trends, products, and business models does the index actually track? For starters, let’s look at the overlap of the index with one of the most popular investments themes in recent years: Digital Health.

18 companies representing 30.5% of NQHTEC’s index weight overlap with the Nasdaq CTA Global Digital Health Index™ (BEWELL™), a single-theme product focusing on pure-play Digital Health companies. Within this subset, a few key sub-themes are well-represented:

1. Telehealth – otherwise known as the ability to “see” a doctor or obtain treatment virtually – whose most well-known player is probably Teladoc Health, the index’s 13th largest holding. Via smartphone or computer, its technology platform enables virtual doctor visits to address short-term as well as chronic medical conditions. Related companies in the index include American Well Corp, Him & Hers Health (with a focus on sexual health), and Lifestance Health Group (with a focus on mental health). Privia Health Group provides a similar service, in addition to other generalized healthcare management services aimed at optimizing physician practices and patient experiences. 1Life Healthcare started out as a differentiated, membership-based provider of in-person primary care; as a function of its growth, it has also invested heavily in delivering virtual care.
2. Connected Medical Devices – sometimes referred to as Wearables – which enable round-the-clock monitoring of a condition and/or on-demand treatment delivery. DexCom, the index’s largest holding, is famous for its glucose monitoring devices for diabetes patients. Similar companies in the index include Tandem Diabetes Care and Insulet (both serving diabetes patients), ResMed (sleep disorders), iRhythm Technologies (heart arrhythmia monitoring), Outset Medical (dialysis), and Masimo (various noninvasive monitoring).
3. Health Data companies, which can offer data platforms, software, cloud solutions, and advanced analytics to healthcare workers, their management, drug companies, and/or patients. Doximity manages a cloud-based platform for medical professionals, while Health Catalyst primarily serves healthcare organizations.
4. Digital Health Benefits Management: GoodRx delivers transparent pricing data and discounts to prescription drug consumers; Progyny targets women specifically for fertility benefits management; Accolade provides personalized health and benefits solutions to improve employer-based healthcare.

Outside of the overlap with BEWELL and Digital Health, there are several other sub-themes within NQHTEC that reflect the powerful, converging trends of digitization, artificial intelligence/machine learning, and bioinformatics within healthcare innovation. In some form or fashion, these trends are all advancing our ability to analyze, model, modify, and even synthesize fundamental building blocks of life such as genes, proteins, chemicals, and cells.

The impacts are clear from an examination of the groundbreaking technologies deployed by companies involved in Genomics. Illumina, the index’s second largest holding, is perhaps the best-known player – not only due to its pioneering work in Next Generation Sequencing (NGS), but also from its earliest days as a startup applying the original Sanger method of sequencing. The rise of NGS transformed genetic sequencing with a massive step function, exponentially reducing its prohibitive costs in terms of both money and time. Illumina’s product portfolio facilitates sequencing from start to finish, providing all the medical instruments, kits and reagents, selection tools, and software to conduct genetic analysis. Per Illumina:

“The critical difference between Sanger sequencing and NGS is sequencing volume. While the Sanger method only sequences a single DNA fragment at a time, NGS is massively parallel, sequencing millions of fragments simultaneously per run. This process translates into sequencing hundreds to thousands of genes at one time. NGS also offers greater discovery power to detect novel or rare variants with deep sequencing.”¹

The upshot is that now, sequencing a human genome takes perhaps 1-2 days and costs less than \$1,000.² Using Sanger sequencing, the original Human Genome Project took around 20 years to complete and cost nearly \$3 billion; in 2007, it still cost around \$10 million.³ Besides Illumina, 10X Genomics, Pacific Biosciences, Fulgent Genetics, and NanoString Technologies also develop tools and solutions for genetic sequencing and analysis. Relatedly, Myriad Genetics, Invitae, and Natera are genetic testing services companies that fall within the broader

¹ <https://www.illumina.com/science/technology/next-generation-sequencing/ngs-vs-sanger-sequencing.html>

² <https://techcrunch.com/2022/03/18/volta-labs-grabs-20-million-to-address-a-growing-genomics-bottleneck/>

³ <https://www.medicaleconomics.com/view/physicians-and-payers-must-embrace-next-generation-genetic-sequencing>

universe of diagnostics; they collect samples and deliver results. Companies like Sema4 can then leverage genomic data by applying AI and machine learning, in conjunction with clinical data, to generate dynamic models of human health with optimal, individualized health trajectories given directly to patients and their doctors.

Advanced understanding of human gene expression will almost certainly drive a historic revolution in our capacity to deliver truly preventative healthcare as well as precision medicine, eventually on a universal scale. In the case of a severe hereditary disease brought on by genetic mutation, gene editing tools may be able to simply “switch off” a physiological malfunction before it brings about a terminal illness (and in some cases, after).⁴ Earlier, more precise screening for genetically-linked cancers – coupled with a much more granular understanding of drug effectiveness across different patient types – will meaningfully improve cancer survival rates. EXACT Sciences (12th largest holding), Guardant Health, NeoGenomics, Veracyte, Castle Biosciences, and Burning Rock Biotech are all oncology-focused screening and diagnostics companies working in this field. In addition, Cytex Biosciences has developed a powerful cell analysis technique called full spectrum flow cytometry, used to advance our understanding of cancerous tumor cells and the immune system.

Beyond targeted cancer screening, companies like QIAGEN (11th largest holding), Quidel, and Quanterix develop advanced molecular tests, digital immunoassays, and analysis tools for a wide array of diseases, enhancing precision medicine across the spectrum from early-stage life sciences research to drug development to clinical diagnostics. Each company’s scope is somewhat unique, with QIAGEN seeking to address the entire “Central Dogma” of molecular biology from DNA to RNA and ultimately, proteins – the final recipient of genetic information in any biological system. Olink and SomaLogic are leading proteomics companies, deepening our understanding of proteins to predict and treat various types of disease. Then there’s Twist Bioscience, which has developed a proprietary, semiconductor-based synthetic DNA manufacturing process. (Among other things, synthetic DNA can be used to store vast quantities of data.) Putting it all together, there is a grand assembly of “multi-omics” research and therapeutic development taking place with the potential to address a wide range of diseases and disorders by some combination of gene editing, gene therapy, direct protein modification, and/or protein targeting via specialized small-molecule drugs.

Finally, NQHTEC also includes companies such as IQVIA (4th largest) and Veeva (10th largest), both of which more closely resemble technology companies, but whose products and services are fully-g geared towards serving the healthcare industry. IQVIA is a data science company with access to over a billion non-identified patient records and a vast global network of data partners (e.g., hospitals, pharmacies, clinical trial investigators, patient networks). They employ thousands of healthcare experts (e.g. medical doctors, epidemiologists) and technologists (statisticians, software developers), along with a proprietary cloud environment leveraging the latest advances in AI/ML, to deliver more than forty commercial offerings to life sciences and healthcare services companies alike.⁵ Veeva is more of a pure cloud services provider, serving life sciences companies across functions from R&D to regulatory/compliance, sales/marketing, and quality/safety. Together, IQVIA and Veeva are ushering every type of healthcare company into the new age of healthcare data.

Putting it all together, perhaps the clearest way of visualizing the breadth of NQHTEC’s exposures is by comparing it with other thematic healthcare products that have recently debuted on the market. The below list of funds is by no means exhaustive, but captures a cross-section of strategies that are broad-based as well as narrowly focused. The two products with the strongest overlap (HTEC & HEAL) also happen to be two of the broadest; still, their portfolios are less than one-third overlapping by weight. Based on number of constituents, NQHTEC’s overlap is less than half (max: 25 out of 59) with each of the six examples. The index draws from multiple thematic exposures while retaining an overall high level of differentiation.

⁴ <https://www.fiercebiotech.com/research/mit-and-ucsf-researchers-create-crispr-off-switch-controls-gene-expression-without>

⁵ <https://ir.iqvia.com/overview/default.aspx>

Ticker	Product Name	# of Constituents	# of Overlap w/ NQHTEC	% Weight Overlap (Own)	% Weight Overlap (NQHTEC)
HTEC	ROBO Global Healthcare and Technology & Innovation ETF	85	25	31.7%	74.7%
HEAL	iShares Healthcare Innovation UCITS ETF	190	22	15.5%	58.5%
EDOC	Global X Telemedicine & Digital Health ETF	38	13	37.1%	27.5%
WDNA	WisdomTree BioRevolution Fund	109	12	7.8%	21.4%
ARKG	ARK Genomic Revolution ETF	49	17	45.4%	16.5%
IDNA	iShares Genomics Immunology & Healthcare ETF	50	2	4.0%	1.1%

Thematic Healthcare ETFs: NQHTEC Overlap as of March 21, 2022

Summary

With the rise in popularity of various thematic healthcare indexes and tracking funds, it is worth evaluating each index methodology, as well as its scope – across companies, technologies, and sub-themes – before making a choice. The NQHTEC Index offers investors the ability to track the intersection of healthcare and technology with a highly differentiated approach leveraging Lux Capital’s long track record and expertise in discovering, evaluating, and funding venture-stage companies at the earliest signs of disruption. The Nasdaq Lux Health Tech Index is a unique strategy that provides exposure to the vanguards of innovation across digital health, biotech (especially genomics), advanced medical devices/diagnostics, life sciences research, and healthcare-specific software and technology solutions companies. In other words: a true union of healthcare and technology.

ETFs currently tracking NQHTEC include the First Trust Nasdaq Lux Digital Health Solutions ETF (Nasdaq: EKG).

Sources: FactSet, Bloomberg, Nasdaq Global Indexes, Lux Capital.

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