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AI In Cough Diagnosis: Making A Vicious Cycle Virtuous

Hyfe Sees Promise In Confluence Of New Molecules And Acoustic AI Technology

by Ashley Yeo

> Hyfe is extending AI to acoustics and championing technology it claims can transform the approach to cough management, leading to improved diagnoses, better treatment and superior health outcomes. CMO Peter Small explained the rationale and how AI has inspired a significant leap forward.

Cough management has always come up short. It is one of the most common reasons people seek healthcare, and yet it has not been measurable. So says Peter Small, chief medical officer at Hyfe, a US-based start-up that is combining artificial intelligence with acoustics.

Hyfe is perfecting a technology to accurately diagnose what is really behind the coughing that sends individuals rushing to their doctor – usually to come away without the answers they seek. Scientists have failed to accurately track coughing for 25 years. "It's not for the want of trying," Small told *In Vivo*.

This ongoing failure has perpetuated a vicious cycle, where patients are unable to convey clearly the nature of their medical condition and clinicians and providers are unable to diagnose the etiology of the cough before them. "There has been no real treatment – it's been very much ignored," the CMO said.

Or worse, it has been the subject of guesswork. Not knowing how bad a cough is might lead a doctor to shoot from the hip and recommend a therapeutic course, the results of which are not always monitored.

The usual routine is that patients not able to describe their condition will often be sent to specialists or a string of clinicians, each of whom is keenly aware that these types of interactions are not always fruitful. Patients tend to come away disappointed or even with feelings of ill will.

But the outlook is improving, and progress is on the cards. "We're in a golden era for cough, with the confluence of COVID-19 and science," Small said. As such, Hyfe's AI-enabled suite of acoustic technologies is a strong component of the new age, new approach to cough management.

A Background In Cough Chasing

The most common causes of cough are asthma, post-nasal drip and reflux, but a decade ago saw the breakthrough realization that cough is not always a symptom of those conditions, but also a disease itself, said Small, who confesses to a 30-year career spent "chasing coughers."

In that time, he has been a UC San Francisco clinician, a researcher using molecular techniques to track tuberculosis at Stanford and later head of the Gates Foundation's global tuberculosis program. He joined Hyfe in 2020.

Small describes Hyfe's technology as having the capability to transform the approach to chronic cough and as being on the cutting edge of acoustic AI and continuous monitoring. The technology has implications for patient empowerment and promises improved diagnosis, better treatment and superior health outcomes, Small believes.

Moreover, Hyfe's breakthrough technology comes at a time of new blockbuster drug activity. No novel cough medicines have been approved by the US Food and Drug Administration for over 60 years. However, _Merck & Co., Inc._ has gefapixant, a P2X3 receptor antagonist, which Small considers as likely to be approved in the US by the end of 2023.

In addition, _GSK plc_'s recent acquisition of Bellus brought with it camlipixant, a potential best-in-class and highly selective P2X3 antagonist currently in Phase III development for the first-line treatment of adult patients with refractory chronic cough. (Also see "_GSK Sees Blockbuster Chronic Cough Opportunity With $2bn Bellus Buyout_" - Scrip, 18 Apr, 2023.)

Hyfe As An End-To-End Cough Company

Small explained: "Where Hyfe stepped in was to recognize the profusion of high-quality microphones and the power of AI. We created a technology that allows continued passive monitoring of cough."

The next piece in the puzzle for Hyfe was the partnership with Actigraph. Combining Hyfe's cough monitoring technology with ActiGraph's LEAP, a wearable smartwatch-like device with a variety of sensors, will provide vast utility to clinicians. "It's a big step in operationalizing Hyfe's

vision and I'm super excited about it," the CMO said. (Also see "*Minute Insight: Hyfe Goes Physical With Wearable Partnership*" - Medtech Insight, 16 Aug, 2023.)

Small continued: "We are an end-to-end cough company – we detect it, provide insights and have launched a program to treat cough with AI-based products. We've partnered with KOLs and have 42 trials worldwide – mostly investigator-initiated – to understand how this technology fits into patient care."

The Hyfe CMO acknowledged that changing clinician behavior can be a "heavy lift," but the company has already reached out to 150 providers and is getting "great feedback" from early adopters.

He said traction is being seen by Hyfe in three areas:

- From its CoughTracker wellness app, which is licensed to Merck & Co in the US (and is known outside the US as CoughPro). The app is free to download and targets the "cough curious." Small said Hyfe was finding receptivity among frustrated patients, who were bringing the technology to the physicians;

- A dedicated wearable that is moving through the FDA. Regulatory clearance for the *de novo* is expected in H1 2024 for monitoring coughs for any etiology in people as they go about their everyday lives; and

- The partnership with Actigraph. "This critical, as they have the 510(k)-cleared LEAP watch –an existing platform into which we are integrating." It will allow pharmas to monitor coughs and other indications.

Small said: "We are excited as it's a chance for us to leap forward in pharma where we are getting lot of traction."

"We're confident this capability with LEAP will be in use by early 2024," Hyfe's CEO and co-founder Joe Brew recently told *Medtech Insight*.

Ongoing Work Around The Future Of Cough

Individuals who download the app will gain a better understanding of their cough when they come into the GP's office, Small explained. They will know its frequency, understand when episodes happened and whether the cough is getting better or worse. The provider will then offer a home-use device to measure it. And there will soon be effective medication. "It will flip this vicious circle into a virtuous one," Small said.

Looking at the big picture perspective, the transformation in cough will make a big difference to

a lot of people's lives, Small predicted. He reiterated: "From a technology perspective, we are extending AI to acoustics, and from a clinical management point of view, it is transforming subjective questions that patients cannot answer into to real continuous data, diagnostics and management."

Papers have been published on clinical utility, but timestamping coughs is the "game changer where most of the impact will come here," Small predicted.

Sound Of The Cough

Some interesting work suggests that the sound of the cough may assist with the diagnosis. Hyfe has submitted a paper done with the Gates Foundation which collected 500,000 coughs from Africa and Asia from presumed TB patients.

"We were able to generate a classifier as a screening test. In under-resourced countries, we can get people to cough into a phone – the future vison is that this will help them know if they should get tested for TB."

Hyfe has also submitted a paper on being able to predict, by the sound of a cough, if someone will have a normal X-ray. This too could be "a game stopper" in poorer countries, where health systems would thus be able to triage patients into normal or abnormal. It might tell the difference between, say, TB and COVID-19. Hyfe's technology and approach are surrounded by a lot of science and regulatory complexity, Small said, "but cough monitoring is a nut we've cracked."

Success At Hyfe In Exploiting AI
Why has Hyfe made the potential breakthrough in this 25-year-long healthcare effort to detect and manage cough? Small explained that prior efforts relied on recording sounds and having people count the coughs, a technique that still persists in most antitussive trials. But these efforts are very intrusive, and highly susceptible to the "Hawthorne effect," Small asserted, noting the supratentorial component.

"What we've done is to exploit the advance in AI. In the world of large language models, our language is explosive sounds. We've been very science-based, collecting over one billion explosive cough-like sounds from all around the world on all kinds of device."

The size and diversity of Hyfe's database helped the company make the breakthrough. Hyfe has hundreds of millions of snippets of audio and has amassed cough and non-cough explosive sounds from men,women, old young, geographically and culturally diverse individuals and both the sick and the healthy. "We are also the world's most nerdy cough company," Small he said

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Research & Method

Hyfe trained the algorithms to distinguish between ambient sounds, including throat clearing, by listening to 20 million coughs. A validation study has showed its accuracy to be 98-99%.

"The story we hear is that when the patient brings the technology to providers, the latter might be dubious at first, but then they see well presented, actionable information – and its value," Small noted.

The technology is rooted in prevention – specifically the prevention of complex medical conditions.

Another paper cited by Small shows clearly that cough is an early indicator of chronic obstructive pulmonary disease (COPD) exacerbation, which is a major cost to health systems. However, the 3.5-day lead time a cough can provide will allow clinicians and providers to forestall these exacerbations and also cut hospital time, said the CMO, adding: "We think the same will be true of asthma."

Where To Next?

Hyfe is seeking to develop more partnerships with pharma companies across the drug development cycle, beginning with pharmacodynamic studies and looking at what dose of which drug reduces cough, using its very precise data.

The company is active in recruiting patients for clinical trials. "We also think we can decrease the placebo effect, which has plagued trials," Small said.

Merck licensed the technology for patient engagement. "Real-world data is huge right now and easily incorporated into patients' lives," Small remarked.

His prediction is that there will be swift developments in the future on cough counting. "Matters will change very quickly, and Actigraph is a big step in that. The device will be available to all – just like blood pressure monitoring devices are," he said. "It's inevitable."

Hyfe is in the process of raising a series A funding, with which it will work towards launch plans.