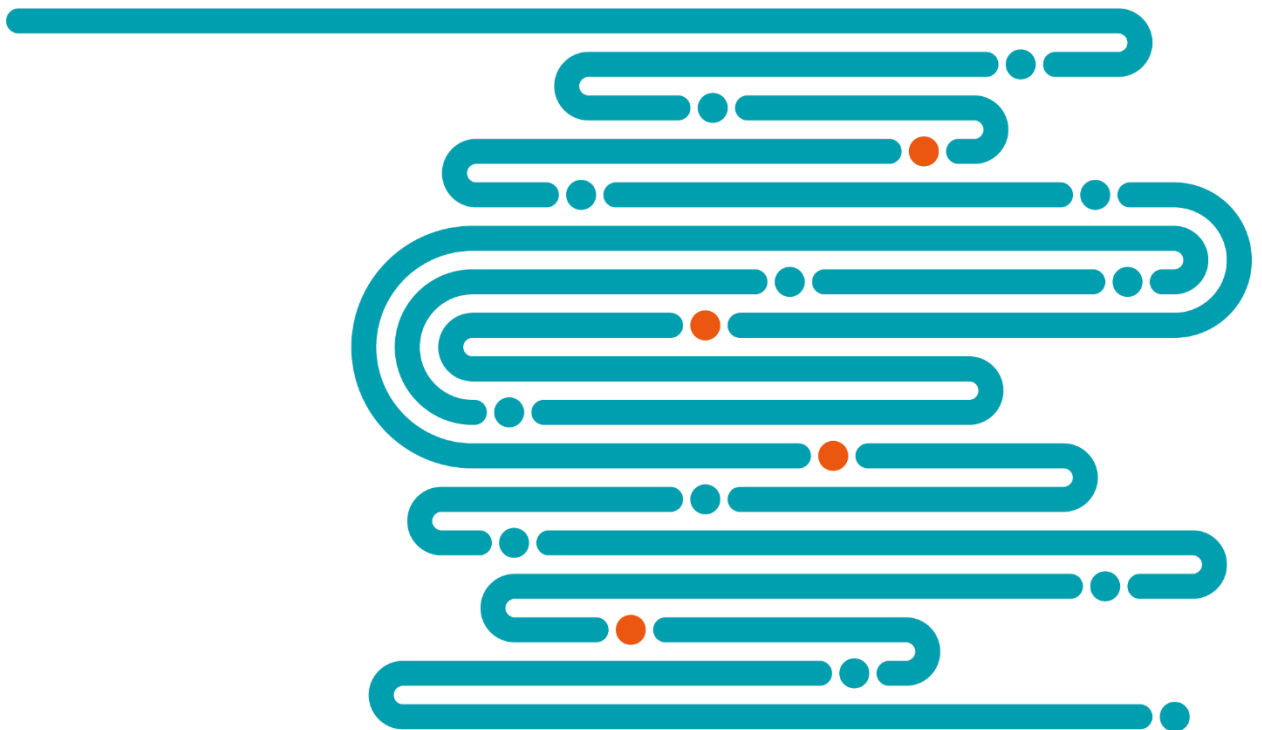


# TechFlash: Devices to assist ventilator weaning in COVID-19 patients

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This report comprises a review of abstracts identified through a search of the recent biomedical literature and does not constitute a comprehensive analysis. The report focus is on clinical evidence and outcomes.



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## Technology overview and status

Mechanical ventilation is often required in seriously ill COVID-19 patients. Weaning patients from the ventilator, however, can be a prolonged process complicated by disuse atrophy of the respiratory muscles. Innovative technologies that reduce the weaning time by helping to recover respiratory muscle strength could improve COVID-19 patient acute outcomes, morbidity, mortality and quality of life (QOL). In addition, these techniques could incrementally help to increase the supply of available ventilators, free up intensive care unit (ICU) beds and reduce overall hospital resource utilization during the pandemic.

The Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) in April and May 2020 to three different medical devices intended to facilitate ventilator weaning. Though none of these were currently FDA cleared for this indication, they were all in various stages of the regulatory process and met criteria for EUA throughout the duration of the declared emergency. The EUA recognizes the lack of rigorous scientific evidence but justifies availability under the caveat that it is “reasonable to believe” they may be effective and that there are no approved alternatives for this indication.

The EUA respiratory assist technologies include the TransAeris Diaphragm Pacing System (Synapse Biomedical; Oberlin, Ohio), the Lungpacer Diaphragm Pacing Therapy System (Lungpacer Medical; Vancouver, Canada) and the VentFree Respiratory Muscle Stimulator (Liberate Medical; Crestwood Kentucky). Though serving a similar purpose, there are unique differences between these devices regarding procedure invasiveness, stimulation target and usage parameters. There are, however, no comparative trials between devices to determine any differences in safety or effectiveness outcomes.

The **TransAeris** DPS consists of an external electrical stimulator, four TransLoc electrodes and associated percutaneous wires (see Figure 1). The electrodes are implanted intramuscularly in the diaphragm using a minimally-invasive laparoscopic approach and left in place for up to 30 days. Synchronized electrical impulses from the stimulator to the electrodes results in diaphragm contraction with secondary muscle strengthening. The electrodes are designed for non-invasive removal similar to that used in a temporary cardiac pacing wire.



Figure 1. TransAeris<sup>®</sup> system. Synapse Biomedical, Inc.

TransAeris is a modified version of the company’s NeuRx<sup>®</sup> diaphragm pacing system used in patients with spinal cord injury (SCI) and amyotrophic lateral sclerosis (ALS). NeuRx has been in development since 2000 and received FDA clearance through a humanitarian device exemption for use in SCI in 2008 and ALS in 2011. More than 2,000 patients have reportedly been treated worldwide with the NeuRx system. TransAeris received a CE Mark allowing European marketing for the ventilator weaning indication in January 2018.

The **Lungpacer** DPTS uses a modified central venous catheter (CVC) with two arrays of electrodes on its surface (see Figure 2). Like a CVC, the LIVE catheter is inserted transvascularily through the left subclavian vein and the electrodes are connected to an external control unit. The electrodes are optimized to stimulate the right and left phrenic nerves where they pass near the vein in route from the brain to the diaphragm. Phrenic nerve activation in turn stimulates the diaphragm to contract. Lungpacer does not have FDA marketing approval, however it received an FDA expedited access pathway designation in 2016 and is currently conducting



Figure 2. Lungpacer<sup>™</sup> catheter. Lungpacer Medical, Inc.

a phase three trial as part of the approval process. A European randomized trial intended for CE Mark submission was completed in January 2020.

The **VentFree** RMS uses an external pulse generator and non-invasive external electrode patches to transcutaneously stimulate abdominal wall muscles rather than the diaphragm (see Figure 3). Targeted muscles include the transversus abdominis and internal and external oblique muscles which assist in exhalation during labored breathing by increasing intra-abdominal pressure. Stimulation is therefore synchronized with exhalation using a flow sensor. This device received an FDA breakthrough device designation intended to expedite approval in January 2019, published results of its pilot trial in July 2019 and received the CE Mark in October 2019.



Figure 3. VentFree™ system. Liberate Medical, LLC.

## Technology significance

Mechanical ventilation is a life-saving therapy in seriously ill COVID-19 patients. Estimates from US hospitals suggest mechanical ventilation may be used in 20% to 30% of patients requiring hospitalization for COVID-19 and 80% to 90% of those in the ICU.<sup>1</sup> The median length of ventilator use is about 10 days, but some with severe disease may require weeks to months of ventilation and ICU stay.<sup>2,3</sup>

Failure to wean from the ventilator after resolution of the primary lung disease is a particularly problematic outcome for COVID-19 patients. Previous studies of critically ill patients on mechanical ventilation have shown about 30% of patients have difficulty weaning that prolongs the duration of ventilation.<sup>4</sup> In these patients, the weaning process itself can account for around 40% of the total time on mechanical ventilation.<sup>5</sup> For example, if the total ventilator usage is 10 days, 4 of those days could be due to the weaning process. More seriously, up to 5% of critically ill patients cannot be easily weaned and therefore may require long-term, chronic ventilator usage. Due to COVID-19 patient demographics that includes high numbers of elderly and patients with existing comorbidities, these rates may be even higher for COVID-19.

Ventilator-induced diaphragm dysfunction (VIDD) is one of the potential causes of prolonged ventilation and/or weaning failure.<sup>6-8</sup> VIDD is characterized by respiratory muscle weakness, reduced contractile force and atrophy of muscle fibers due to disuse because the ventilator is doing most of the work of breathing. VIDD is noted to occur after as little as 18 to 24 hours on a ventilator. Similar processes likely occur in the other respiratory associated muscles as well.<sup>9</sup>

Reversal of VIDD and/or rehabilitation of the respiratory muscles is the goal of the technologies described in this report. Potential advantages associated with the use of these technologies may include:

- Shorter time on the ventilator
- Fewer ventilator-associated complications (e.g., pneumonia, pressure injury)
- Shorter ICU stays
- Increased rate of extubation
- Better long-term outcomes
- Increased quality of life

Decreased resource utilization during surge conditions is an additional potential benefit. For example, the FDA EUA posited a potential for decreasing ventilator use, and therefore increasing ventilator capacity, by ~26% using diaphragm stimulation technologies. This approximation was based on an average ventilator use of 10 days, average weaning time of 4 days and an estimated 64.5% reduction in weaning time associated with diaphragm pacing. In this hypothetical scenario, diaphragm pacing could reduce the weaning time by 2.6 days ( $2.6 / 10 = 26\%$  potential savings).

Disadvantages associated with this technology may include increased device and procedural costs, complications associated with the implantation/removal procedure and adverse events during operation. Further, there are still many unproven assumptions about its safety, acceptability, evidence quality and efficacy. This is typical of emerging technology, like these, in the early pre-approval stages of development and particularly for technology being rapidly implemented during a crisis.

## Current practice and alternatives

Conventional weaning from mechanical ventilation in critically-ill patients is a well-established process initiated following adequate resolution of the underlying respiratory disease when the patient meets certain criteria for lung function under reduced ventilator settings.<sup>10,11</sup> Spontaneous breathing trials (SBTs) lasting 30 to 120 minutes with minimal to no ventilator support are used to determine final readiness for extubation in addition to weighing the potential risk for complications and/or reintubation. Weaning can take days to weeks depending on a complex set of disease course and patient-specific variables. Longer ventilator times usually require longer weaning times.

In patients with weaning difficulties, a multi-disciplinary approach focused on nutritional support, physiotherapy and psychological preparation may be needed.<sup>4</sup> Ventilator protocols may involve progressive reduction of ventilator support and/or longer SBTs so that the patient rebuilds natural breathing impulses and strength.<sup>5</sup> In cooperative alert patients, coached deep breathing exercises with resistive therapy may be used to rebuild respiratory muscle strength.<sup>12</sup> Treating complicating co-morbidities, like cardiac, neuromuscular, endocrine and metabolic changes associated with critical care, is also frequently needed to facilitate weaning.

Ventilator weaning usually takes place in the ICU setting. However, regions experiencing patient surges during the COVID-19 pandemic may have severely limited ICU capacity. Depending on hospital organization, personnel and resources, an in-hospital “step-down” intermediate-care respiratory weaning and rehabilitation unit may be one option for difficult-to-wean patients as well as recently extubated patients.<sup>2</sup> Ideally, this alternative would provide the multi-disciplinary care needed to facilitate weaning. Transfer of patients to highly-specialized regional weaning centers with experienced and well-trained teams, access to advanced technologies and provision of multi-disciplinary services may also be an option for hard-to-wean patients.<sup>4</sup> Failure-to-wean patients are often eventually transferred to specialized long-term care facilities.

Placement of a tracheostomy may be considered in COVID-19 patients expected to require prolonged ventilation.<sup>13-15</sup> Tracheostomy may also facilitate weaning and potentially increase ICU bed capacity. Optimal timing, definitive indications and outcomes for tracheostomy, however, are not well defined in COVID-19 patients.

## Clinical evidence summary

The [Medline/PubMed](#) bibliographic database, [MedRxiv](#) preprint server for health sciences, Google COVID-19 [Research Explorer](#) and [ClinicalTrials.gov](#) database of registered clinical studies were searched in July 2020 to identify clinical evidence on the use of devices to assist ventilator weaning. Keywords used in the search strategy included: *VentFree, abdominal functional electrical stimulation, Lungpacer, LIVE catheter, phrenic nerve stimulator/stimulation, temporary transvenous diaphragmatic neurostimulation, temporary transvenous diaphragm pacing, TransAeris, TransLoc and diaphragm pacing electrodes.*

The literature search found no published studies pertaining to these technologies used to assist ventilator weaning in COVID-19 patients. Two articles in the gray literature have reported anecdotal use of diaphragm pacing in COVID-19 patients at University Medical Centers in Greifswald Germany (Lungpacer) and Cleveland Ohio (TransAeris).<sup>16, 17</sup> At this point in time, the available clinical evidence consists mostly of reports from pre-approval phase 1 or 2 clinical studies with use in non-COVID patients. In general, the clinical evidence-base is of low quality and limited by study design, short-term follow-up, small patient numbers and lack of concurrent control groups.

Permanent diaphragm pacing has been studied for use in SCI and ALS for more than 20 years.<sup>18-28</sup> Primary evidence consists of mostly small, manufacturer-sponsored prospective and retrospective case series. Overall, safety analyses show the implantation procedure to be well tolerated with risks similar to those associated with other comparable surgical procedures. High rates of successful stimulation, long-term usage and high weaning rates have been reported in SCI and ALS patients.

Temporary diaphragm pacing using the TransAeris system has been studied in two U.S. feasibility trials enrolling 12 patients ([NCT02410798](#)) and 40 patients ([NCT04309123](#)) at University Hospitals Cleveland Medical Center. The targeted population in these studies were elective surgical patients expected to have difficulty weaning from the ventilator after surgery. The electrodes were implanted following the index surgery; thus, patients did not have to undergo a separate surgical procedure for implantation. Due to design modifications to the temporary electrodes, removal is accomplished by pulling the lines without the need for a surgical procedure.

The early feasibility trial of the TransAeris system showed successful implantation and stability of all electrodes until removal after up to seven days.<sup>29</sup> Functional stimulation of the diaphragm sufficient to prevent atrophy was reported. However, ventilator parameters and weaning outcomes were not studied in this feasibility trial. The larger trial has not yet reported results, but primary completion is expected by December 2020.<sup>30</sup>

The Lungpacer system has been studied for ventilator weaning in a series of trials called RESCUE-1 ([NCT03107949](#)), RESCUE-2 ([NCT03096639](#)), and RESCUE-3 ([NCT03783884](#)). RESCUE-1 was a nine-patient feasibility trial, RESCUE-2 is a randomized controlled trial (RCT) of 110 patients conducted in France and Germany and RESCUE-3 is a multi-center RCT expected to enroll up to 376 patients. So far, RESCUE-1 has been completed and published, RESCUE-2 has published the study design and reportedly completed the trial in January 2020, though the results are not yet published, and RESCUE-3 is ongoing with the first patient enrolled in June 2019 and final results not expected until 2021 or 2022.<sup>31-33</sup>

RESCUE-1 was a multi-center, open-label study of the Lungpacer LIVE catheter used in adult ICU patients on mechanical ventilation for more than seven days and who had failed two weaning trials.<sup>34</sup> Eleven patients met entry criteria and nine had successful catheter insertion with effective capture of the phrenic nerves and

stimulation of diaphragmatic contractions. Weaning was accomplished within the 30-day study duration in 78% (7/9) of patients. The mean duration of diaphragm pacing was 16.7 days. Another feasibility type trial (NCT02670460) of the Lungpacer system showed successful stimulation of the left phrenic nerve in 96% (22/23) and right phrenic nerve in 87% (20/23) of cases.<sup>35</sup>

Abdominal functional electrical stimulation has been studied in a number of basic science studies and for improving clinical outcomes, like cough, in mechanically ventilated SCI patients.<sup>36-41</sup> In a study of ten SCI patients (NCT02200393), tidal volume and vital capacity were incrementally increased using a regimen of abdominal stimulation.<sup>36</sup> These patients reportedly could be weaned on average 11 days faster than patients from a matched cohort.

Use of the VentFree device has been studied for ventilator weaning in ICU patients in two small 20-patient RCTs conducted in the Europe (NCT03453944) and Australia (ACTRN12617001180303). In the Australian study, ICU length of stay (median, 11 days vs. not estimable days, P = 0.011) and ventilation duration (median, 6.5 days vs. 34 days, P = 0.039) were shorter in the treatment group compared to controls.<sup>42</sup> However, small patient numbers limit the precision of the estimated difference. Further, no difference in abdominal muscle thickness was noted between groups. No serious adverse events associated with device usage were reported.

## Financial issues

The financial justification for the use of technologies to assist in ventilator weaning may be based on offsetting upfront technology costs by reducing days on mechanical ventilation and ICU days. ICU costs may average about \$5,000 per day and the incremental cost of mechanical ventilation in ICU patients may be about \$1,500 per day.<sup>43</sup> In addition, every day on a ventilator increases the risk of ventilator-associated pneumonia. This complication can add weeks to the hospital LOS and direct costs exceeding \$12,000.<sup>44</sup> Extubation failure may be associated with costs for tracheostomy and long-term care facilities and nursing care. These cumulative costs can readily exceed \$100,000 per year.

Because they are in the early stages of development, however, there remain many unknowns surrounding the clinical and economic outcomes for these technologies. Further study is needed, therefore, to better delineate the inputs for financial modeling. Similarly, these technologies may be associated with improved mortality and QOL. However, rigorous calculations of cost-effectiveness cannot be made yet because of the lack of comparative efficacy outcomes data.

## Patient selection criteria

The indication listed in the FDA EUAs suggest use of this technology is intended for COVID-19 patients on mechanical ventilation who have been determined to be at high risk of weaning failure.<sup>45</sup> Specific criteria, however, have not been defined and the management decision is generally left up to the discretion of the healthcare provider to be made on a case-by-case basis. Table 1 shows some of the criteria associated with prolonged weaning times that may be factored into usage decisions.

Clinical trial patient enrollment criteria are also not specific to COVID-19 at this stage of development. For the Lungpacer device, the RESCUE-2 and RESCUE-3 trials have inclusion criteria for mechanical ventilation  $\geq$  four days, satisfied readiness-to-wean criteria and failed at least two SBTs.<sup>31, 33</sup> Exclusion criteria involve extracorporeal membrane oxygenation, hypervolemia, congestive heart failure, body mass index  $\geq$  40, known phrenic nerve paralysis and less than 6-months life expectancy.

The optimal timing for device use in COVID-19 patients is also unknown. These devices can be used early in the disease course, even when the patient is sedated and unable to cooperate. This may be advantageous because muscle wasting is known to begin within the first day on mechanical ventilation. However, the invasiveness of some of the procedures suggest waiting for more information on the expected resolution of the underlying respiratory disease and viral clearance, which can be two to three weeks in COVID-19 patients, and better evaluation of potential weaning difficulty.

Table 1. Factors associated with prolonged weaning.<sup>4</sup>

<b>Categorization</b>	<b>Potential factors</b>
<b>Systemic</b>	Chronic diseases, comorbidities, nutrition and metabolic disturbances, severity of illness
<b>Cardiovascular</b>	Left ventricular dysfunction, myocardial ischemia, cardiomyopathy
<b>Neurologic</b>	Critical illness neuromuscular abnormalities
<b>Respiratory</b>	Unresolved causes of respiratory failure, imbalance due to respiratory muscle capacity, upper airway obstruction
<b>Cognitive</b>	Delirium, depression and anxiety, sleep deprivation
<b>Treatment complications</b>	Ventilator-associated pneumonitis and infections, barotrauma, tracheostomy, sedation
<b>Treatment setting</b>	Weaning protocols, staffing, staff training

### Future developments

Continued development of clinical evidence is expected and needed in the near future. There is some evidence from yet to be published, pre-pandemic clinical trials that may help to define the effect of these devices on key outcomes of interest, like weaning success, adverse events, hospital and ICU LOS, mortality and QOL.

Furthermore, though well-designed and conducted trials require a significant amount of time, the pandemic has accelerated many phases of the clinical trial process, including rapid patient enrollment and early pre-print publication of interim results. In this accelerated timeframe, more clinical data on use specifically in COVID-19 patients may be expected in late 2020. This data may be limited to case studies and small case series and some may come from European sites, but results could help to better determine potential efficacy, patient selection criteria and appropriate usage.

Beyond COVID-19, this technology may have a high impact on the problem of prolonged ventilator weaning in critically ill and surgical patients. By one estimate, this population comprises more than 625,000 patients annually in the US and accounts for \$64 billion in healthcare costs.<sup>46</sup> Even a small improvement applied to this large population could significantly effect hospital and patient outcomes. This is why these technologies were originally granted expedited/breakthrough status by the FDA. Full FDA approval, however, is not expected until 2021 or 2022, depending on the technology and trial results.



## Conclusions and recommendations

The following conclusions and recommendations are based on the material presented in this report:

- Three different technologies have been cleared through the FDA EUA process as potentially useful to assist ventilator weaning in COVID-19 patients. None were previously approved for this purpose, but they were all pursuing FDA approval and in various stages of development. Diaphragm pacing has had limited use for other indications for decades and some of the technologies are available for use in Europe.
- Acquired respiratory muscle weakness due to mechanical ventilation is one of the potential causes of prolonged weaning. Similar to physical therapy, electrical stimulation of the diaphragm or other breathing pump muscles can help to rebuild strength and facilitate weaning from mechanical ventilation. Successful use could reduce time on the ventilator, ICU LOS, hospital LOS, secondary pneumonia, rates of extubation failure and overall morbidity and mortality.
- The evidence-base for these technologies when used to facilitate weaning in COVID-19 patients is very limited. It is mostly derived from pre-pandemic early stage trials in other types of illness. These studies have shown that the technology can capture and stimulate contractions in the respiratory muscles. The effect on weaning outcomes, however, is not well proven. Usage decisions are therefore based mostly on clinical expertise and opinion.
- The ICU is one of the most high-cost, resource-intensive settings in the hospital. Therefore, reducing ICU LOS has the potential to provide significant savings. Unfortunately, there is not enough comparative data on weaning outcomes at this time to determine the cost benefit of these technologies.
- Appropriate patient selection may be the key to rational clinical use. Many factors may be involved in the etiology of prolonged ventilation with difficulty weaning. Conservative patient selection should be applied due to the limited evidence available to assist decision-making.
- Prolonged ventilator weaning is well-known to be problematic in a diverse group of patients and indications. Future use of these technologies beyond the pandemic is likely following more rigorous approval standards.

## Related links

Company websites: [Liberate Medical](#), [Lungpacer Medical](#), [Synapse Biomedical](#)

FDA EUA [list](#)

FDA EUA letter	Information sheets	Instructions for use
<a href="#">Liberate Medical VentFree Respiratory Muscle Stimulator Device</a>	<a href="#">Healthcare Providers</a> <a href="#">Patients</a>	<a href="#">IFU - Model A</a> <a href="#">IFU - Model B</a>
<a href="#">Lungpacer Medical Diaphragm Pacing Therapy System</a>	<a href="#">Healthcare Providers</a> <a href="#">Patients</a>	<a href="#">IFU, Live Catheter Kit</a> <a href="#">IFU Handheld Controller</a> <a href="#">IFU</a>
<a href="#">Synapse Biomedical TransAeris Diaphragmatic Pacing Therapy System</a>	<a href="#">Healthcare Providers</a> <a href="#">Patients</a>	<a href="#">IFU</a> <a href="#">Surgical Procedures</a> <a href="#">IFU</a>

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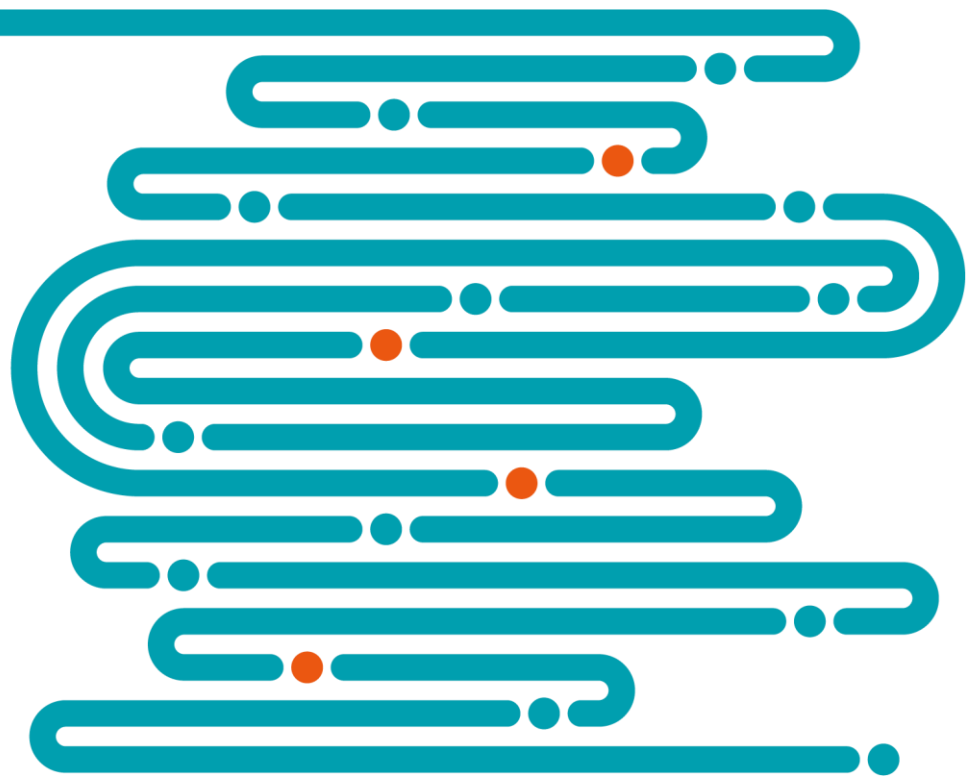
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