

Synapse

4th Edition

Recurrent Implantation Failure (RIF)



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Recurrent implantation failure (RIF) is a clinical concern primarily associated with patients undergoing assisted reproductive technologies (ART). True RIF is relatively uncommon, occurring in less than 5% of couples experiencing infertility. RIF is largely over diagnosed and overtreated, often without sufficient critical evaluation of its underlying etiology.

At present, there is no universally accepted definition of RIF. However, the most widely endorsed criteria stem from the 2022 Lugano RIF Workshop (1), which defines RIF as the failure to achieve a clinical pregnancy following the transfer of at least three euploid blastocysts, or an equivalent number of unscreened embryos adjusted for maternal age and corresponding euploidy rates, as detailed in Table 1 of the consensus report.¹

Estimation model for of the number of unscreened good-quality embryos needed to be equivalent to 3 successive euploid embryo transfers and achieve a 95% chance of sustained implantation on the basis of the observed aneuploidy rate ⁽²⁰⁾		
Age (y)	Observed aneuploidy rate	No. of untested blastocysts to achieve a 95% chance of sustained implantation
<35	20%	4
35–37	30%	5
38–40	50%	7
41–42	70%	13
≥ 43	85%	27

Recurrent implantation failure. Fertil Steril 2023.

The failure of embryo implantation is multifactorial in nature and may result from embryonic, uterine, paternal, or procedural factors, including the specific in vitro fertilization (IVF) protocol employed. These contributing factors are explored in detail in the following sections.

- **Maternal Age** - As maternal age increases aneuploidy increases because of increased chromosomal nondisjunction.² There is decrease in mitochondrial membrane potential, increase of mitochondrial DNA damage and higher rates of embryo-endometrial asynchrony with increasing maternal age thus leading to decreased implantation rate and live birth rate after 35 years of age.
- **BMI** -The oocyte quality and follicular development might be affected by obesity. The implantation rate decreases with increasing BMI (>25 kg/m²).
- **Smoking** -Cigarette toxins such as carbon monoxide causes depletion of oxygen to the fetus, and nicotine leads to vasoconstriction and decreased nutrients to the fetus, thus implantation may be impaired.
- **Stress** -Elevated levels of cortisol, also known as “the stress hormone,” lead to a 2.7 times greater chance (95% CI=1.2–6.2) of miscarriage within the first 3 weeks after conception in comparison with women with low cortisol levels. However this has been refuted by studies that it is IVF failure that may lead to higher rates of both anxiety and depression in the immediate period after a negative IVF outcome.³

Pathophysiological mechanisms of Recurrent Implantation Failure

Based on the definition proposed above, RIF is primarily due to uterine factors. However there will inevitably be a proportion of cases due to gamete or embryo factors.

- **Oocyte Factor:** The response to ovarian stimulation might be poor with fewer numbers of oocytes retrieved, a high proportion of immature oocytes, reduced fertilization rate. High FSH and low anti-Mullerian hormone, points to poor oocyte quality. Age related aneuploidy increases as age advances. Aggressive ovarian stimulation protocols may lead to poor-quality oocytes and a higher rate of fertilization failure.⁴
- **Sperm Factor:** Semen analysis doesn't reflect sperm quality. Sperm DNA damage (caused by cigarette smoking, genital tract infection and previous chemotherapy or radiotherapy) is associated with poor embryo development.⁵
- **Genetics/ Parental chromosomes anomaly:** Chromosomal abnormalities like translocations, mosaicism, inversions, and deletions(translocation being most common) may lead to RIF though the overall prevalence is only about 2%.⁶ Parental karyotyping is recommended in cases of women suffering from RIF and in men with severe oligospermia.
- **Thrombophilia:** Whether hypercoagulable state leads to RIF is still debatable however prothrombotic disorders are more prevalent in RIF patients than in controls. While patients with RIF who have prothrombotic disorder might benefit from heparin treatment, for those without this abnormality empiric treatment with heparin is not justifiable.⁷ Altogether, it is recommended that patients diagnosed with RIF be investigated for acquired as well as hereditary thrombophilia disorders, and be treated accordingly.

- **Immunological Causes:** Differentiation of endometrial stromal cells(a process called decidualization), is critical for the establishment and maintenance of pregnancy. The decidualized stromal cells acquire the ability to regulate trophoblast invasion and to dampen local maternal immune responses.⁸ There is much conflicting evidence in the literature on the role of immunological factors like peripheral and uterine natural killer cells , Th1/Th2 ratio and TNF- α levels in women with RIF . There is no consensus on whether or not immunological investigations are useful and whether immunological treatment is of benefit.
- **Anatomical abnormalities and endometrial thickness:** Uterine pathologies including polyps, myomas, and adhesions can impact implantation rates in patients undergoing IVF. The anomalies can be congenital and acquired.

Congenital Uterine Pathology

- Myomas -can cause distortion of the endometrial cavity
- Septate Uterus – Most common congenital anomaly. The poor outcome is related to the distortion of the uterine cavity and to the inadequate blood supply to the septum
- Bicornuate Uterus – Women with a bicornuate uterus usually have normal implantation, but these patients have a higher risk of mid trimester pregnancy loss . These patients usually don't require surgery
- Hydrosalpinx -The fluid can negatively impact endometrial receptivity, and can also physically flush the embryo out preventing implantation.

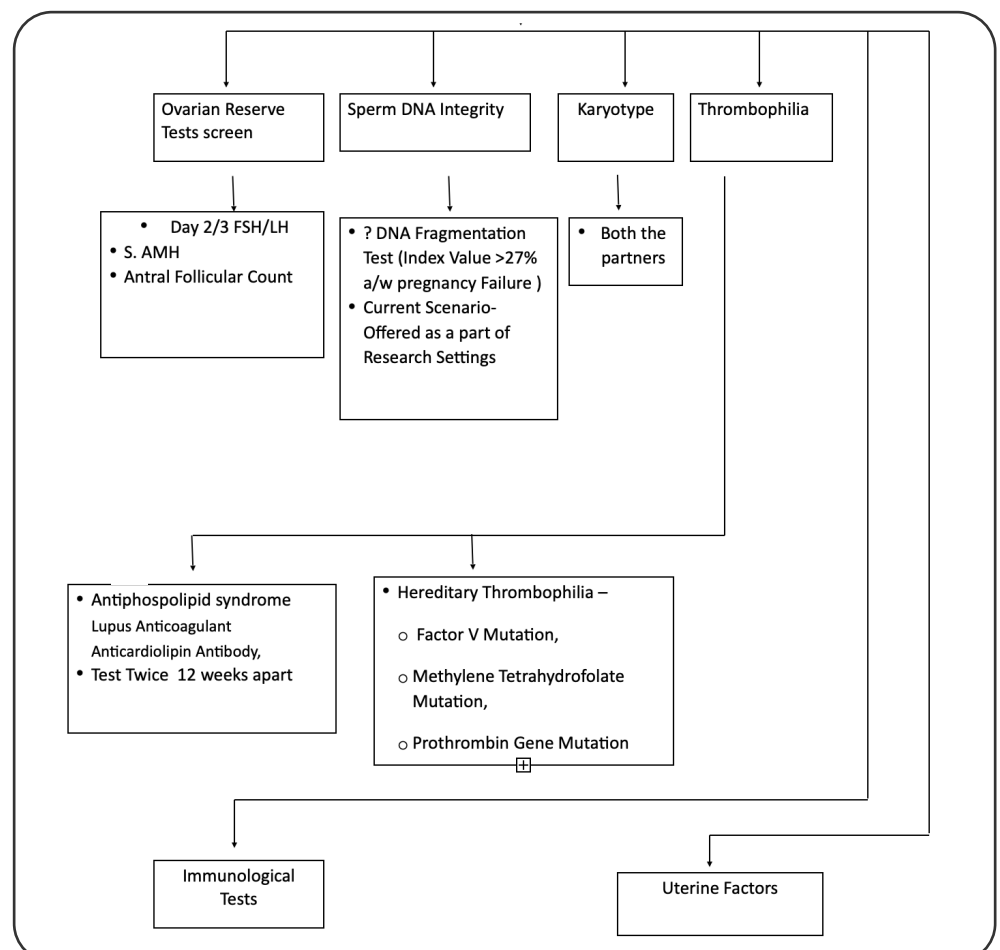
Acquired Uterine Pathology

- Frequency of unrecognized intrauterine pathologies in patients with RIF varies between 25% and 50%.⁹
 - Endometrial Polyp : Endometrial polyps may interfere with embryo implantation . The removal of endometrial polyps has been found to result in improved spontaneous pregnancy rates in various studies.
 - Intrauterine adhesions. Adhesions within the uterine cavity may prevent the embryos from attaching to the luminal surface of the endometrium. Intrauterine adhesions often occur following curettage of the gravid uterus to terminate an unwanted pregnancy or in cases of retained products of conception after a pregnancy or miscarriage.
 - Adenomyosis - Adenomyosis affects the junctional zone of the uterus which is just beneath the endometrium and thus implantation is affected . Unlike intramural fibroids, adenomyosis is not usually amenable to surgical treatment .
 - Submucous and Intramural fibroids. The submucous and intramural fibroids of > 4cm may adversely affect implantation by increasing uterine contractility, deranged cytokine profile, abnormal vascularization and chronic endometrial inflammation.
- **Thin endometrium** - Thin endometrium (<7 mm) may occur following damage to the endometrium following intrauterine surgery or infection and may lead to RIF. Hysteroscopy adhesiolysis is recommended by an experienced reproductive surgeon.

Flow Chart of Investigations

Investigations

The investigations for the RIF need to be individualized after taking a detailed history and checking the previous records . Broad Outline of the investigations is mentioned in the table below.



Multidisciplinary approach should be adopted in the management of a couple with RIF. Appropriate counselling and individualized treatment of the couple with RIF is of the utmost importance prior to proceeding with further treatment. A brief overview of current treatment strategies for RIF is outlined below.

1. **Lifestyle modifications:** The European Society of Human Reproduction and Embryology (ESHRE) recommends several lifestyle interventions that may positively influence outcomes in individuals experiencing recurrent implantation failure (RIF). These include smoking cessation support, adoption of a balanced and nutritious diet, engagement in regular physical activity, and prioritization of mental health and psychological well-being. Such modifications, while not specific to RIF, may contribute to improved reproductive outcomes and overall health.
2. **Optimal IVF-ET Protocols:** An appropriate controlled ovarian hyperstimulation (COH) protocol is essential, especially in patients with a history of suboptimal response. It's important to review prior cycle outcomes and adjust the stimulation protocol and gonadotropin dosage accordingly. In a study by Barmat et al¹⁰ no significant difference in implantation rates was observed between the long GnRH agonist and antagonist protocols. However, the antagonist protocol was found to be more convenient for patients, primarily due to the shorter duration of the treatment cycle and timing of oocyte retrieval.
3. **Embryo transfer**
 - A. **Cleavage vs Blastocyst Transfer:** With advances in culture media and lab techniques, blastocyst transfer has become the preferred approach over cleavage-stage transfer, showing higher implantation rates, irrespective of embryo quality. However, this strategy may not benefit all patients equally. Some studies have overgeneralized their findings to broader populations and are not restricted to RIF. Factors such as age, ovarian reserve, lab conditions, and sperm quality should guide the decision. A 2016 Cochrane review¹¹ found only low- to moderate-quality evidence supporting blastocyst transfer over cleavage-stage transfer for improving live birth and clinical pregnancy rates.
 - B. **Frozen embryo transfer vs Fresh embryo transfer:** While frozen embryo transfer (FET) is gaining popularity—partly due to concerns about the altered hormonal environment and impaired endometrial receptivity in stimulated cycles—it's still a topic of ongoing debate. FET has been linked to lower risks of preterm birth, low birthweight, and OHSS. However, evidence on its superiority remains mixed. A large meta-analysis by Roque et al¹² reported no significant benefit in live birth or cumulative live birth rates among normo-responders. These findings suggest that a “freeze-all” approach may not be appropriate for every IVF patient.
 - C. **Embryo transfer Method:** Ultrasound-guided embryo transfer improves clinical pregnancy and live birth rates. The choice between a soft or rigid catheter often depends on the shape of the cervix. In some cases, gently removing cervical mucus by aspiration can also boost the chances of pregnancy.
4. **Progesterone support:** Progesterone support is important in improving birth rates for patients with repeated implantation failure (RIF). A systematic review by Saccone et al¹³ confirmed that progesterone in early pregnancy benefits women with recurrent pregnancy loss. Vaginal, intramuscular, and subcutaneous routes are all effective. Additionally, oral dydrogesterone is found to be as effective as vaginal progesterone for luteal support in IVF patients.
5. **Immunotherapy:** Maternal-fetal immune tolerance is a necessary condition for successful implantation. Several immunological therapies have been explored to increase implantation rates. Endometrial biopsies and peripheral blood sampling for NK cell type and count or Th cell proportion offer a method to assess maternal immune status and a rationale for immune-modulating therapies
 - A. **Glucocorticoids** act as immunomodulators by binding to receptors on uterine natural killer (uNK) cells and reducing their numbers. They may improve implantation rates in patients with elevated peripheral CD69+ NK cells. However, while prednisolone can lower uNK cell levels, it has not shown a clear benefit on pregnancy outcomes. Therefore, glucocorticoids should be used cautiously, tailored to specific cases, as optimal dosage and timing remain uncertain.
 - B. **Intravenous immunoglobulin** IVIG therapy is considered for women with repeated implantation failure who show immune imbalances like elevated Th1/Th2 ratio, increased NK cells, abnormal TNF- α /IL-10 ratio, or autoantibodies. It helps normalize the Th1/Th2 balance, increases regulatory T cells, and reduces NK cell numbers and activity.¹⁴ IVIG is typically given at 200–500 mg/kg (usually 400 mg/kg) about 7 days to 24 hours before embryo transfer and continued either until fetal heartbeat is detected or every three weeks during pregnancy.
 - C. **Tacrolimus**, an immunosuppressant approved for transplant rejection, has been explored as a treatment for RIF patients with elevated Th1/Th2 ratios. It works by inhibiting cytotoxic T cell activity, lymphocyte proliferation, and the production of IL-2 and IFN- γ .¹⁵ However, more research is needed to confirm its effectiveness and to establish safe dosing for RIF patients.
 - D. **Intralipid Therapy:** Intralipids are fat emulsions that can modulate natural killer (NK) cell activity and reduce inflammation. However, a study using 20% intralipid infusion on embryo transfer day showed no improvement in pregnancy or live birth rates. Coulam¹⁶ suggested intralipids may benefit only RIF patients with specific immune abnormalities, highlighting the need to identify these cases. Overall, evidence is insufficient to recommend routine intralipid use, and no standardized treatment protocol exists.
 - E. **Lymphocyte immunization therapy:** Lymphocyte Immunotherapy (LIT) involves administering partner-derived lymphocytes to modulate the maternal-fetal immune balance. However, the 2017 ESHRE guidelines do not recommend LIT for patients with recurrent pregnancy loss due to limited evidence and potential risks, including infections, autoimmune reactions, and irregular antibody formation.

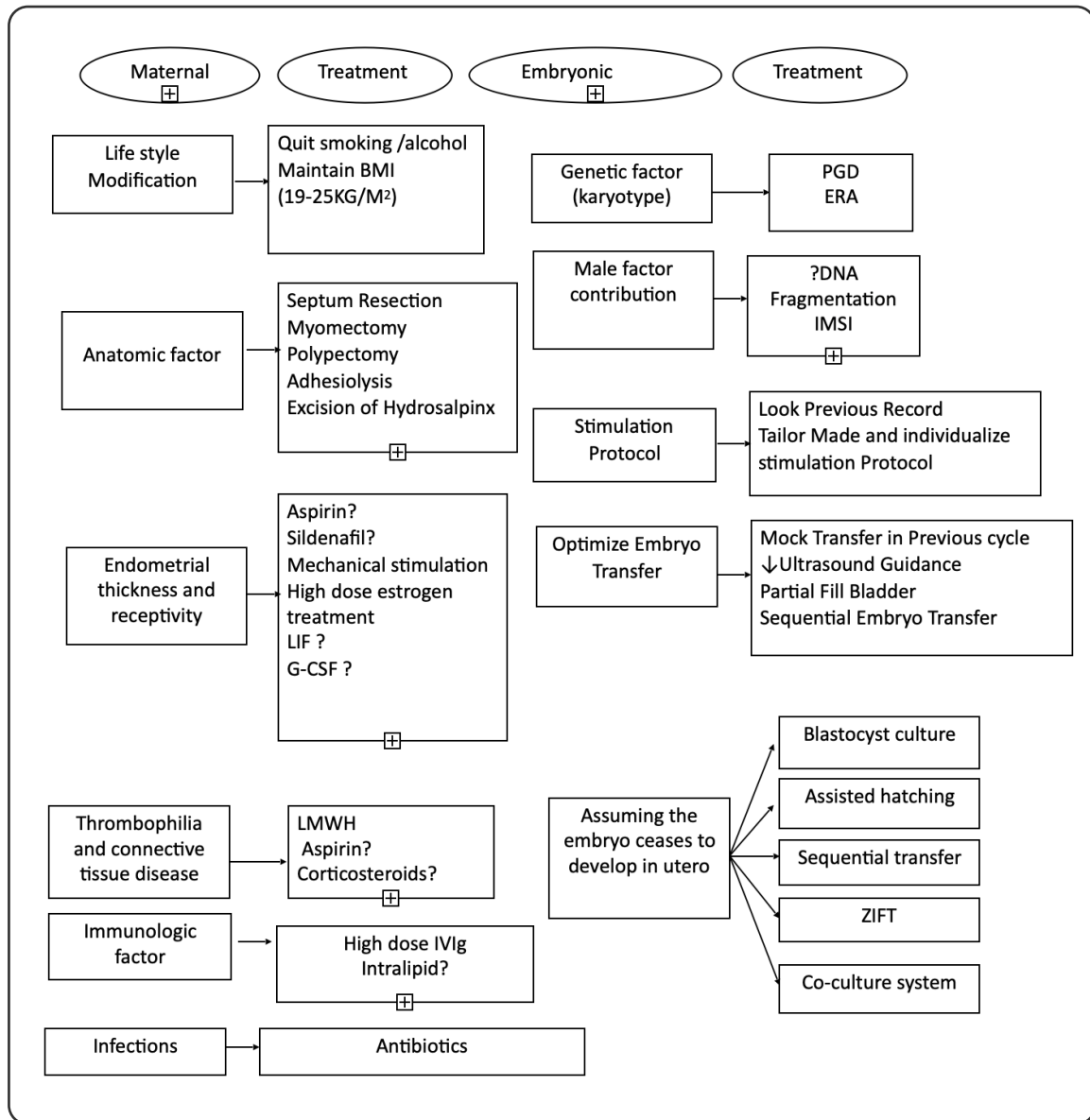
6. **Anticoagulants:** Aspirin, by inhibiting cyclooxygenase, acts as an antithrombotic and may reduce uterine inflammation and improve blood flow, potentially enhancing endometrial receptivity. However, studies in RIF patients have shown no significant improvement in implantation or pregnancy rates compared to controls.¹⁷A. LMWH Low molecular weight heparin
 - A. (LMWH) has anticoagulant effects that may help prevent placental thrombosis and support endometrial function. In patients with multiple unexplained failed embryo transfers, LMWH (40 mg/day) started after oocyte retrieval showed a trend toward higher live birth rates but no significant difference in implantation or pregnancy outcomes.¹⁸
7. **Intrauterine infusion**
 - A. A. Platelet-rich plasma: Platelet-rich plasma (PRP) is an autologous blood product rich in growth factors that promote angiogenesis, cell growth, and immune modulation. In patients with repeated implantation failure (RIF), PRP has shown promise in improving endometrial thickness and clinical pregnancy rates. However, larger, high-quality studies are needed to confirm its effectiveness and safety.¹⁹
 - B. Granulocyte colony-stimulating factor-Granulocyte-colony stimulating factor (G-CSF) is a cytokine produced by various cells, including endothelial and immune cells. However, randomized controlled trials and meta-analyses have shown that intrauterine G-CSF infusion does not improve implantation or pregnancy rates in patients with repeated implantation failure.¹⁹
8. **Endometrial scratching:** Endometrial scratching, which intentionally injures the lining to release cytokines like LIF and IL-11 important for implantation, has been proposed as a treatment but currently lacks proven effectiveness.
9. **Endometrial receptivity assay:** The Endometrial Receptivity Assay (ERA) aims to personalize embryo transfer timing in patients with repeated implantation failure (RIF). While some recent studies report improved pregnancy and live birth rates with ERA-guided transfers, evidence remains inconsistent. Multiple randomized trials and meta-analyses show no significant benefit, and current guidelines (e.g., ESHRE)²⁰ (do not support its routine use. ERA may be considered in selected cases, but broader RIF management should prioritize embryo quality, endometrial optimization, and treatment of underlying pathology. Further research is needed to clarify ERA's clinical value.²¹
10. **Preimplantation Genetic Testing for Aneuploidy (PGT-A):** Preimplantation Genetic Testing for Aneuploidy (PGT-A) is used to identify chromosomally normal (euploid) embryos prior to transfer, with the goal of improving implantation and live birth rates. In patients with repeated implantation failure (RIF), PGT-A may help distinguish between embryonic and endometrial causes of failure.

Several studies support the use of PGT-A in RIF, especially in women of advanced maternal age or those with multiple failed IVF cycles. A meta-analysis by Chen et al.²² found that PGT-A significantly increased clinical pregnancy and live birth rates in RIF patients.

However, some randomized controlled trials (RCTs), including the STAR trial²³ have shown mixed results in the general IVF population, with limited benefit from PGT-A in younger women or those with good prognosis. As such, current guidelines recommend PGT-A selectively for RIF patients, particularly when aneuploidy risk is high

While PGT-A does not address endometrial or immunological causes of RIF, it is considered a valuable tool for optimizing embryo selection and reducing time to pregnancy in appropriate cases.
11. **Antibiotics:** Studies show that treating chronic endometritis with oral antibiotics significantly improves pregnancy and live birth rates compared to untreated cases. A recent meta-analysis also confirmed higher implantation and clinical pregnancy rates in patients whose infection was cured. However, combining oral antibiotics with intrauterine infusion of antibiotics did not improve outcomes and may disrupt the intrauterine environment.²⁴
12. **Hysteroscopy:** Polyps, myomas, adhesions, and septa can all affect implantation, and the gold standard for evaluation is hysteroscopy. The previously reported prevalence of undetected anomalies was between 20 and 45%, however, Fatemi et al. found the prevalence in their study population to be only 11%, identifying polyps as the most common pathology (41%).²⁵ Hysteroscopy might serve as a useful diagnostic tool in many RIF patients, as some literature suggests that with this intervention there can be major changes in pregnancy outcome.
13. **Male factor:** Sperm morphology may influence repeated implantation failure (RIF). Intracytoplasmic morphologically selected sperm injection (IMSI), which uses high magnification to select sperm before injection, showed higher implantation 19.2% vs. 7.8%, $P = 0.042$, pregnancy 43.1% vs. 10.5%, $P = 0.02$, and live birth rates 43.1% vs. 10.5%, $P = 0.02$ in one retrospective study by Shalom-Paz et al.²⁶ However, other studies have not confirmed these benefits. More research is needed before IMSI can be recommended as a standard procedure.

Table 2: A summary of the management is highlighted



Summary

Recurrent Implantation Failure (RIF) is a multifactorial condition with diverse etiologies and treatment options. The most effective approach appears to be personalized medicine, tailored to each patient's unique profile. While no single treatment fits all, standardized preliminary testing could guide individualized management. Future well-designed studies are essential to develop evidence-based protocols and improve outcomes.

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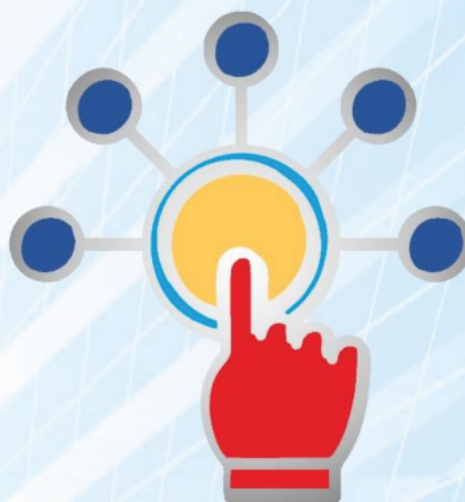
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